

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problems Mailbox.**

EUROPEAN PATENT APPLICATION

Application number: 85108132.3

Int. Cl.⁴: **C 07 D 487/04**
A 61 K 31/40, C 07 D 519/00

Date of filing: 01.07.85

Priority: 02.07.84 US 626821

Date of publication of application:
05.02.86 Bulletin 86/6

Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

Applicant: **MERCK & CO. INC.**
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065(US)

Inventor: **Christensen, Burton G.**
770 Anderson Avenue, Apt. 19H
Cliffside Park New Jersey 07010(US)

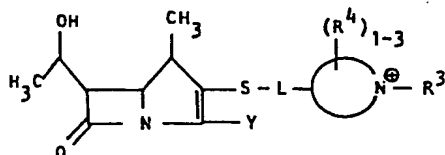
Inventor: **Johnston, David B.R.**
53 Round Top Road
Warren New Jersey 07060(US)

Inventor: **Schmitt, Susan M.**
50 M Southwyck Village
Scotch Plains New Jersey 07076(US)

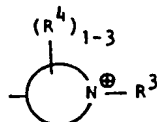
Representative: **Abitz, Walter, Dr.-Ing. et al,**
Abitz, Morf, Gritschneider, Freiherr von Wittgenstein
Postfach 86 01 09
D-8000 München 86(DE)

1-Methylcarbapenems having an externally alkylated mono- or bicyclic 2-quaternary heteroarylalkylthio substituent.

Carbapenems having the formula:



wherein



is a mono- or bicyclic quaternary heteroaryl, their preparation and antibiotic use are disclosed.

-2-

166221cy

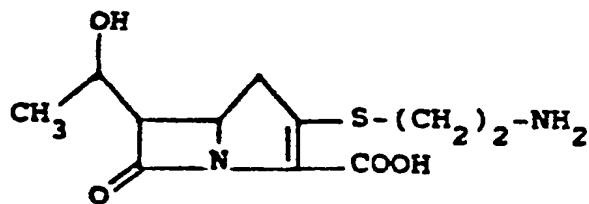
TITLE OF THE INVENTION

1-METHYLCARBAPENEMS HAVING AN EXTERNALLY
ALKYLATED MONO- OR BICYCLIC 2-QUATERNARY HETERO-
ARYLALKYLTHIO SUBSTITUENT

BACKGROUND OF THE INVENTION

The present invention is concerned with carbapenems antibiotics having a quaternary mono- or bicyclic heteroaryl containing group in the 2-position and a methyl group in the 1-position.

Thienamycin is a known carbapenem, broad spectrum antibiotic of the formula:



2360P/0840A

-3-

2361P/0840A

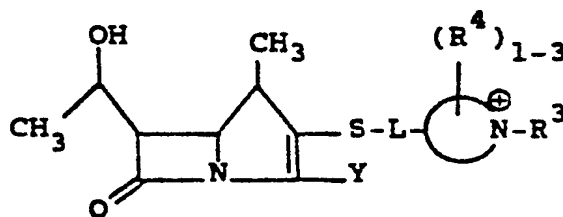
16622IH

Other derivatives of A are also known.

The present externally alkylated mono- or bicyclic 2-quaternary heteroarylalkylthio substituted carbapenems have an antibiotic spectrum equal to or better than A. The present carbapenems also are more resistant than A to degradation by the dehydro-peptidase enzyme DHP-I. The present carbapenems are also more resistant to DHP-I mediated degradation and are chemically more stable, both in solution and in the solid state, than the corresponding carbapenems lacking the 1-methyl substituent.

SUMMARY OF THE INVENTION

Carbapenems having the formula:



I

wherein R^3 is a quaternizing substituent, R^4 is a ring hydrogen or substituent, L is a covalent bond

or a bridging group,  is mono- or bicyclic heteroaryl, and

Y is a carboxy containing substituent.

2360P/0840A

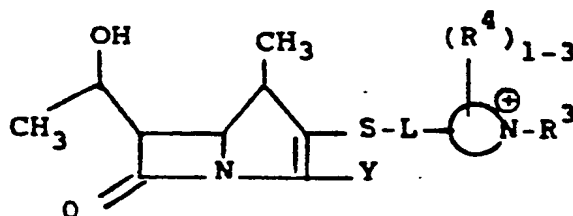
-4-

2361P/0840A

16622IH

DETAILED DESCRIPTION OF THE INVENTION

The invention is embodied in a compound having the formula:



wherein:

L is a covalent bond or a bridging group selected from $-(CH_2)_{1-4}S-$; $-(CH_2)_{1-4}O-$;

15 $-(CH_2)_{1-4}X-(CH_2)_{1-4}$ where X=O, S, NH, or $N(C_1-C_6)$ alkyl; substituted or unsubstituted C_1-C_4 straight, C_1-C_6 branched or C_3-C_7 cycloalkyl groups wherein the substituents are selected from

20 C_1-C_6 alkyl, $O-C_1-C_6$ alkyl, $S-C_1-C_6$ alkyl, halo, OH, CF_3 , CN, NH_2 , NHC_1-C_6 alkyl, $N(C_1-C_6$ alkyl) $_2$, CO_2H , $CONH_2$, $CONH(C_1-C_6$ alkyl), and $CON(C_1-C_6$ alkyl) $_2$;

25 is a mono- or bicyclic heteroaryl cation group

30 containing from 5-11 ring atoms of which up to 5 are heteroatoms wherein R^3 is:

- 1) an unsubstituted or substituted C_1-C_6 alkyl radical;
- 2) an unsubstituted or substituted C_1-C_6 alkenyl radical;

2360P/0840A

-5-

2361P/0840A

16622IH

- 3) an unsubstituted or substituted
C₁-C₆ alkynyl radical;
- 4) a C₃-C₇ cycloalkyl radical in which
the ring is substituted or
5 unsubstituted and one or more atoms may
be replaced by a heteroatom;
- 5) a C₃-C₇ cycloalkyl methyl radical
in which the ring may be substituted
and one or more atoms may be replaced
10 by a heteroatom;
- 6) an unsubstituted or substituted
C₅-C₇ cycloalkenyl radical;
- 7) an unsubstituted or substituted
bivalent C₂-C₆ alkylidene radical,
15 optionally interrupted by a heteroatom,
and joined to the heteroarylium group
to form a ring which is carbocyclic or
in which one or more atoms is replaced
by a heteroatom. The new ring may
20 contain one or more double bonds;
- 8) an unsubstituted or substituted phenyl
or heteroaryl radical;
- 9) an unsubstituted or substituted phenyl
(C₁-C₄ alkyl) or heteroaryl
25 (C₁-C₄ alkyl) radical;
- 10) a cyano (C₁-C₄ alkyl) radical;
- 11) a carbamoyl (C₁-C₄ alkyl) radical;
30
- 12) a hydroxy (C₁-C₄ alkyl) radical;
- 13) an amino (C₁-C₄ alkyl) radical in
which the nitrogen atom is
unsubstituted or substituted with one
to three C₁-C₄ alkyl groups;

-6-

16622IH

14) an acidic side-chain of the structure

$-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

$n = 0-4$

$m = 0-4$

$X = CHR^3, CH=CH, \text{phenylene } (-C_6H_4-), NH, N(C1-C4 \text{ alkyl}),$
 $O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;$
 $R^3 = H, O(C1-C4 \text{ alkyl}), NH_2, NH(C1-C4 \text{ alkyl}), N(C1-C4 \text{ alkyl})_2,$
 $CN, CONH_2, CON(C1-C4 \text{ alkyl})_2, CO_2H, SO_2NH_2,$
 $SO_2NH(C1-C4 \text{ alkyl});$

$Y = \text{single bond}, NH, N(C1-C4 \text{ alkyl}), O, S;$

$A = \text{an acidic function such as carboxy } (CO_2H),$
 $\text{phosphono } [P=O(OH)_2], \text{alkylphosphono } \{P=O(OH)-$
 $[C(C_1-C_4 \text{ alkyl})]\}, \text{alkylphosphinyl } [P=O(OH)-$
 $(C_1-C_4 \text{ alkyl})], \text{substituted phosphoramido}$
 $[P=O(OH)NH(C_1-C_4 \text{ alkyl}) \text{ and } P=O(OH)NHR^X],$
 $\text{sulfinio } (SO_2H), \text{sulfo } (SO_3H), \text{5-tetrazolyl}$
 $(CN_4H), \text{arylsulfonamido } (SO_2NHR^X) \text{ and acylsul-}$
 $\text{fonamides represented by the structures}$
 $CONHSO_2(C_1-C_4 \text{ alkyl}), CONHSO_2N(C_1-C_4 \text{ alkyl})_2 -$
 $SO_2NHCO(C_1-C_4 \text{ alkyl}) \text{ and } SO_2NHCOR^X;$

$R^X = \text{aryl or heteroaryl as defined above};$

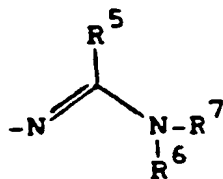
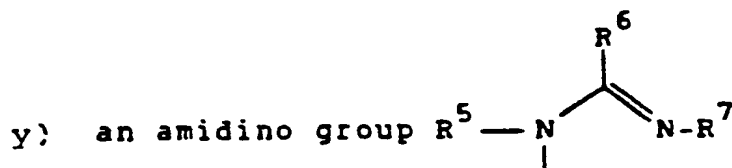
wherein the substituents in the above definitions of R^3 are independently selected from the group consisting of the definitions of R^4 set out below;

R^4 is independently selected from:

- a) a trifluoromethyl group;
- b) a halogen atom;
- c) an unsubstituted or substituted C_1-C_4 alkoxy radical;
- d) a hydroxy group;
- e) an unsubstituted or substituted $(C_1-C_6 \text{ alkyl})$ carbonyloxy radical;

- f) a carbamoyloxy radical which is unsubstituted or substituted on nitrogen with one or two C_1-C_4 alkyl groups;
- g) a C_1-C_6 alkylthio radical, C_1-C_6 alkylsulfinyl radical or C_1-C_6 alkylsulfonyl radical, each of which is unsubstituted or substituted on the alkyl group;
- h) a sulfamoyl group which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;
- i) an amino group;
- j) a mono (C_1-C_4 alkyl) amino or di(C_1-C_4 alkyl)amino group, each of which is unsubstituted or substituted on the alkyl group;
- k) a formylamino group;
- l) an unsubstituted or substituted (C_1-C_6 alkyl)carbonylamino radical;
- m) a (C_1-C_4 alkoxy) carbonylamino radical;
- n) a ureido group in which the terminal nitrogen is unsubstituted or substituted with one or two C_1-C_4 alkyl groups;
- o) a (C_1-C_6 alkyl)sulfonamido group;
- p) a cyano group;
- q) a formyl or acetalized formyl radical;
- r) an unsubstituted or substituted (C_1-C_6 alkyl)carbonyl radical wherein the carbonyl is free or acetalized;
- s) an unsubstituted or substituted phenylcarbonyl or heteroarylcarbonyl radical;

- t) a hydroximinomethyl radical in which the oxygen or carbon atom is optionally substituted by a C_1-C_4 alkyl group;
- u) a (C_1-C_6 alkoxy)carbonyl radical;
- v) a carbamoyl radical which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;
- w) an N-hydroxycarbamoyl or $N(C_1-C_4$ alkoxy)carbamoyl radical in which the nitrogen atom may be additionally substituted by a C_1-C_4 alkyl group;
- x) a thiocarbamoyl group;



where R^5 , R^6 and R^7 are independently hydrogen, C_1-C_4 alkyl or wherein two of the alkyl groups together form a C_2-C_6 alkylidene radical optionally interrupted by a heteroatom and joined together to form a ring;

- z) a carboxamidino group $\begin{array}{c} NR^5 \\ || \\ C \\ \diagup \quad \diagdown \\ \quad \quad NR^6 R^7 \end{array}$. where R^5 , R^6 and R^7 are as defined above;

- 5 aa) a guanidinyll group where R^6 in ab) above is NR^8R^9 and R^8 and R^9 are as defined for R^5 through R^7 above.
- ab) hydrogen;
- ac) an unsubstituted or substituted C_1-C_6 alkyl radical;
- 10 ad) an unsubstituted or substituted C_1-C_6 alkenyl radical;
- ae) an unsubstituted or substituted C_1-C_6 alkynyl radical;
- af) a C_3-C_7 cycloalkyl radical in which the ring is substituted or unsubstituted and one or more atoms may be replaced by a heteroatom;
- 15 ag) a C_3-C_7 cycloalkyl methyl radical in which the ring may be substituted and one or more atoms may be replaced by a heteroatom;
- 20 ah) an unsubstituted or substituted C_5-C_7 cycloalkenyl radical;
- ai) an unsubstituted or substituted phenyl or heteroaryl radical;
- aj) an unsubstituted or substituted phenyl (C_1-C_4 alkyl) or heteroaryl (C_1-C_4 alkyl) radical; and
- 25 ak) an acidic side-chain of the structure
- A or $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:
- 30 $n = 0-4$
- $m = 0-4$
- $X = CHR^5, CH=CH, \text{phenylene } (-C_6H_4-), NH, N(C1-C4 \text{ alkyl}), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;$
- $R^5 = H, O(C1-C4 \text{ alkyl}), NH_2, NH(C1-C4 \text{ alkyl}), N(C1-C4 \text{ alkyl}), CN, CONH_2, CON(C1-C4 \text{ alkyl}), CO_2H, SO_2NH_2,$
- 35 $SO_2NH(C1-C4 \text{ alkyl});$
- $Y = \text{single bond}, NH, N(C1-C4 \text{ alkyl}), O, S;$

-10-

A = an acidic function such as carboxy (CO_2H), phosphono [$\text{P}=\text{O}(\text{OH})_2$], alkylphosphono [$\text{P}=\text{O}(\text{OH})-\text{C}(\text{C}_1-\text{C}_4 \text{ alkyl})$], alkylphosphinyl [$\text{P}=\text{O}(\text{OH})-\text{C}(\text{C}_1-\text{C}_4 \text{ alkyl})$], substituted phosphoramido [$\text{P}=\text{O}(\text{OH})\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$ and $\text{P}=\text{O}(\text{OH})\text{NHP}^X$], sulfino (SO_2H), sulfo (SO_3H), 5-tetrazolyl (CN_4H), arylsulfonamido (SO_2NHR^X) and acylsulfonamides represented by the structures $\text{CONHSO}_2(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{CONHSO}_2\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})_2$, $\text{SO}_2\text{NHCO}(\text{C}_1-\text{C}_4 \text{ alkyl})$ and $\text{SO}_2\text{NHCOR}^X$;

R^X = aryl or heteroaryl as defined above;

- Y is selected from:
- i) COOH or a pharmaceutically acceptable ester or salt thereof.
 - ii) COOR^1 wherein R^1 is a removable carboxy protecting group.
 - iii) COOM wherein M is an alkali metal, or
 - iv) COO^\ominus ; provided that when Y is other than iv) a counterion Z^\ominus is provided.

As used herein, the term "heteroatom" means nitrogen, oxygen, or sulfur, independently selected where more than one heteroatom is involved.

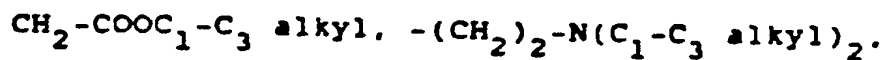
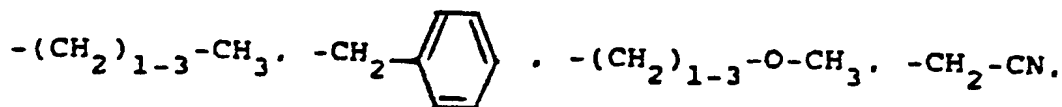
Representative L groups are $-\text{CH}_2-$.

- $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{C}_2\text{H}_5)-$, $-(\text{CH}_2)_{2-4}$,
- $-\text{CH}(\text{CH}_3)-\text{CH}_2-$, $\text{CH}_2-\text{CH}(\text{OCH}_3)-$,
- $-\text{CH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-\text{CH}(\text{CH}_2\text{OH})-\text{CH}_2-$,
- $-\text{CH}(\text{CF}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{S}$, $-\text{CH}_2-\text{CH}_2-\text{O}$,
- $-(\text{CH}_2)_2-\text{S}-\text{CH}_2-$, $-(\text{CH}_2)_2-\text{O}-\text{CH}_2$, a single covalent bond, and the like.

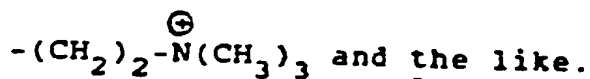
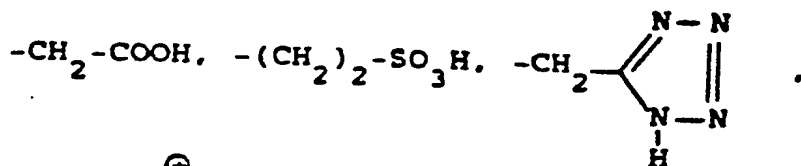
A preferred L group is a substituted or unsubstituted C₁-C₆ linear or branched chain alkyl. A more preferred L group is -CH₂-, -CH(CH₃)- or (CH₂)₂-.

Examples of useful R³ groups are -CH₃.

5



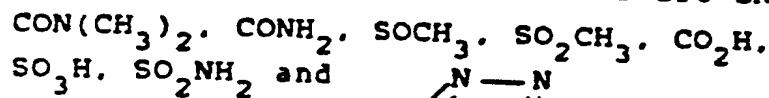
10



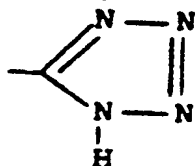
15

Preferred R³ groups are the C₁-C₆ alkyls, both substituted and unsubstituted.

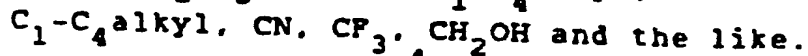
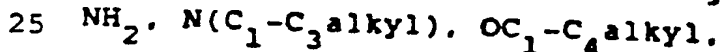
Preferred substituents are CN,



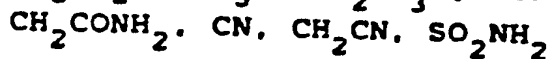
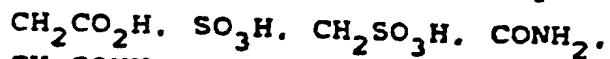
20



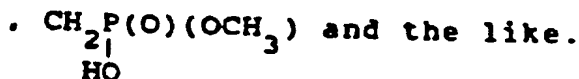
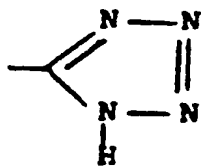
Examples of useful R⁴ groups are OH,



Preferred R⁴ groups are CO₂H,



30



2360P/0840A

2361P/0840A

-12-

16622IH

The - moiety is mono- or bicyclic

quaternary heteroaryl group having 5-11 ring atoms of which, in addition to the quaternary N⁺, up to four can be heteroatoms.

5

Of particular interest and the most preferred group are compounds of the present invention wherein the substituent on the N-containing mono- or bicyclic quaternary heteroaryl group in the 2-
10 position is an acidic function as defined above and the Y substituent in the 3-position is COO⁻ as defined above, thus forming a zwitterion with the positive charge of the quaternary nitrogen. The acidic function is anionic and the compounds
15 are thus anionic zwitterions, i.e., they have a net negative charge. This novel characteristic has been found to result in at least one surprising and important improvement in the biological properties of the compounds reduced CNS side-effects.
20 A more particular group of the compounds, those wherein the acidic function is a sulfoalkyl group of the formula (C₁₋₄ alkyl)SO₃⁻, have been found to have the additional surprising and important biological property of enhanced potency against Pseudomonas
25 species, an especially important nosocomial pathogen. In this most preferred group of compounds, it is preferred that the N-containing mono- or bicyclic quaternary heteroaryl group in the 2-position is pyridinium.

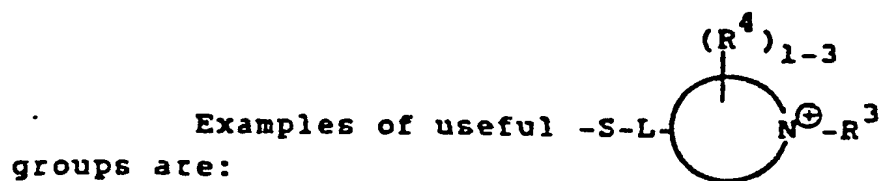
30

2360P/0840A

2361P/0840A

-13-

16622IH



5

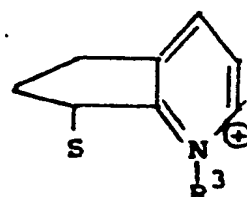
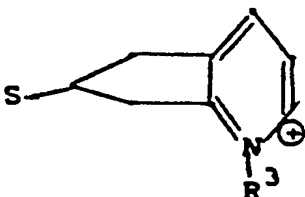
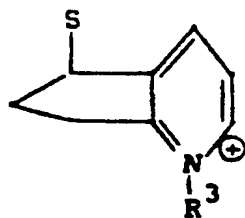
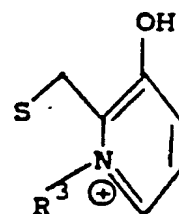
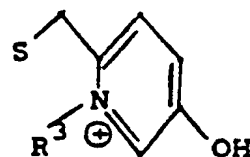
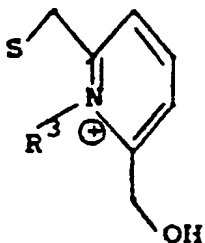
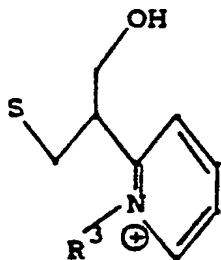
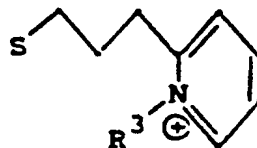
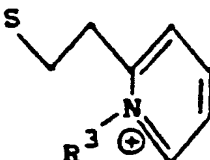
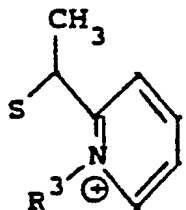
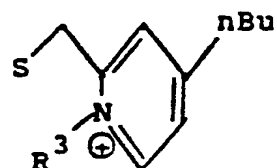
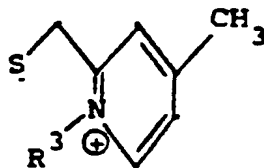
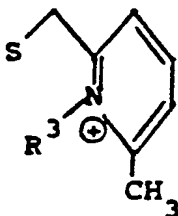
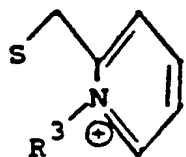
10

15

20

25

30

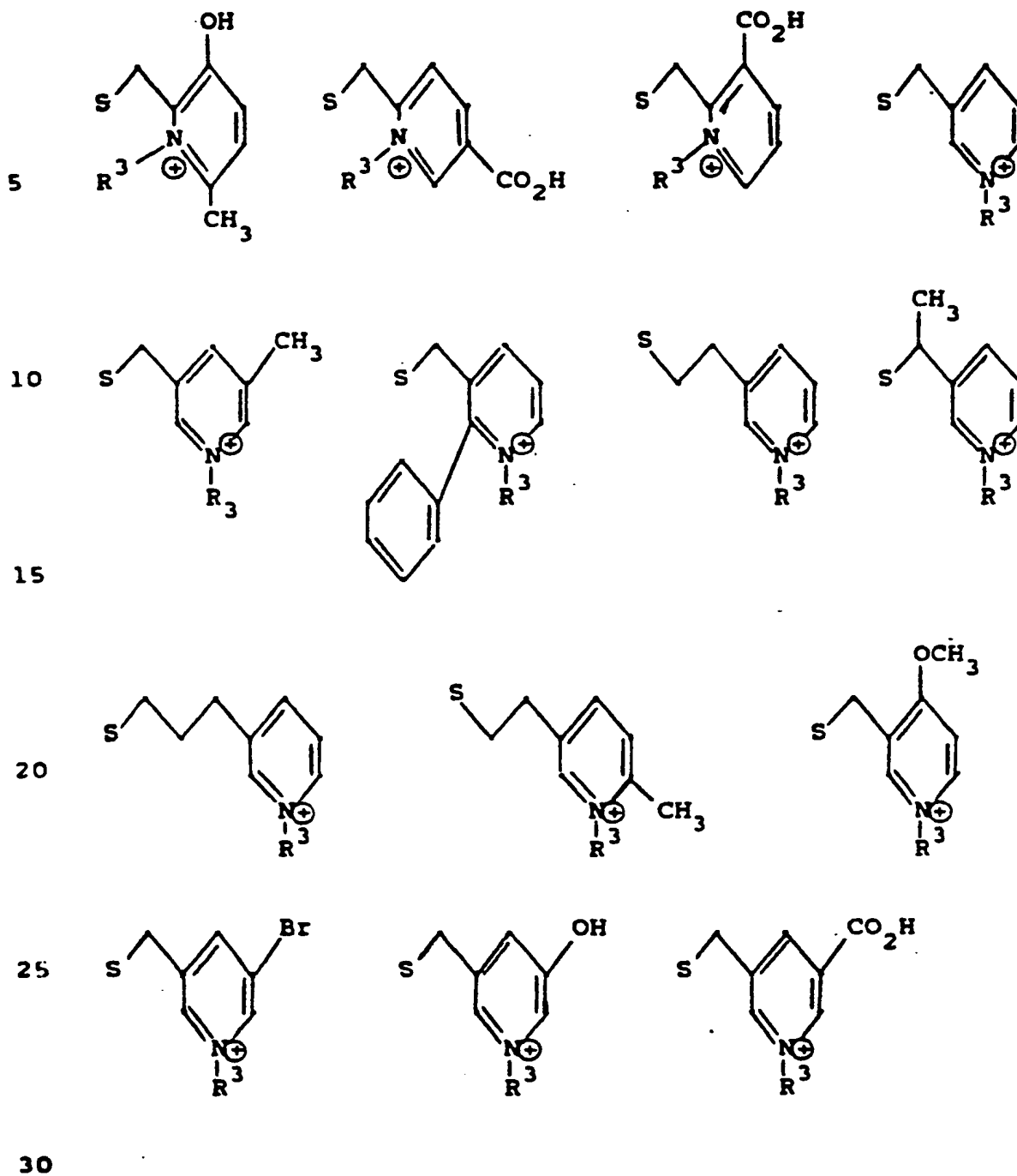


2360P/0840A

2361P/0840A

-14-

16622IH

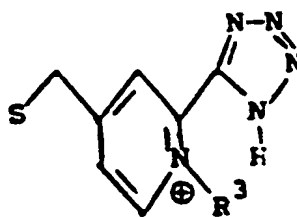
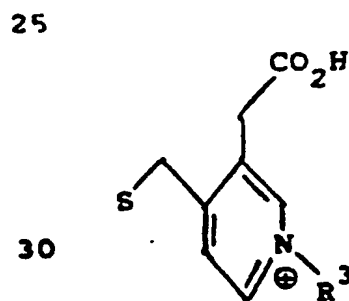
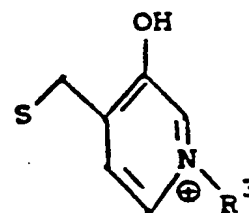
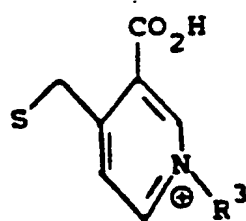
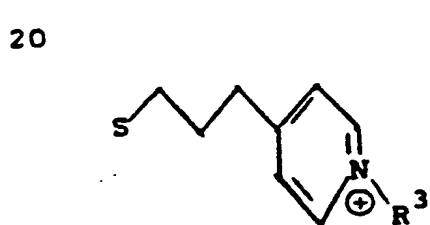
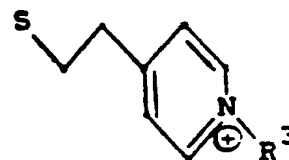
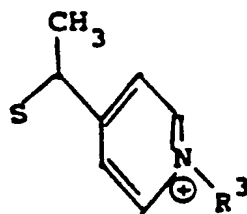
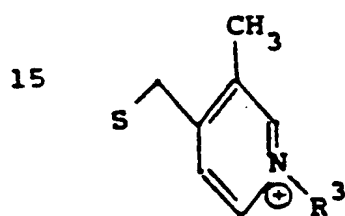
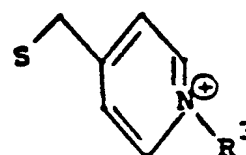
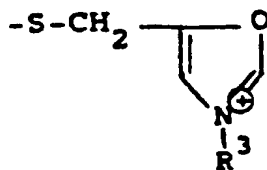
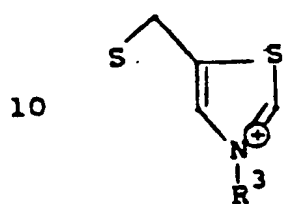
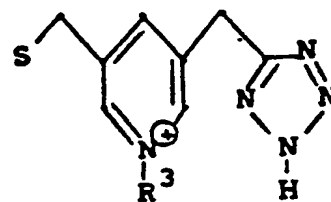
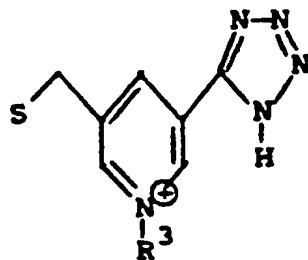
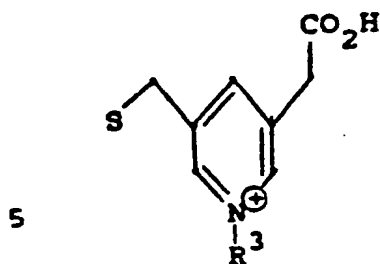


2360P/0840A

2361P/0840A

-15-

16622IH



30

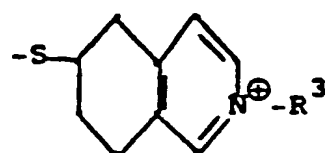
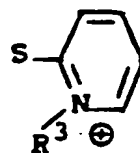
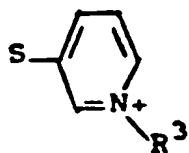
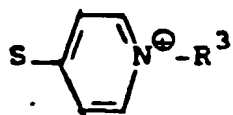
2360P/0840A

2361P/0840A

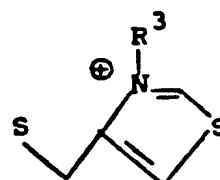
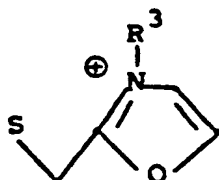
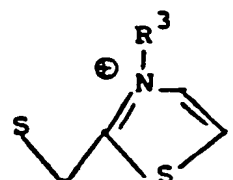
-16-

16622IH

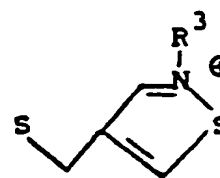
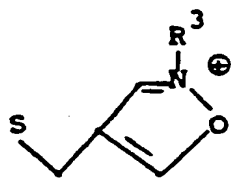
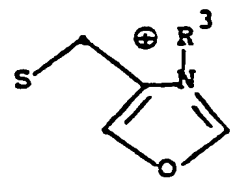
5



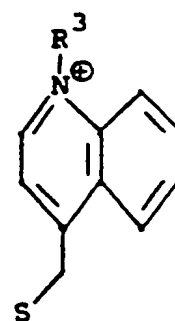
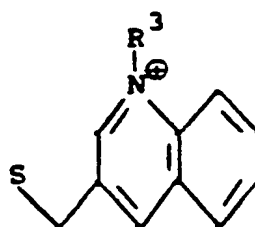
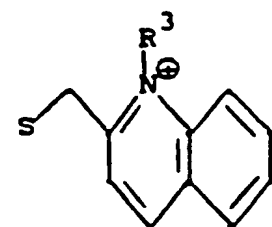
10



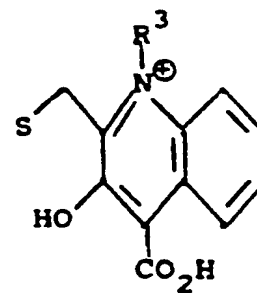
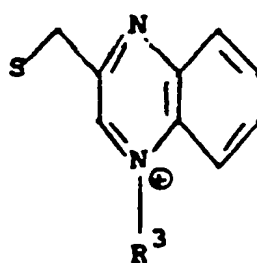
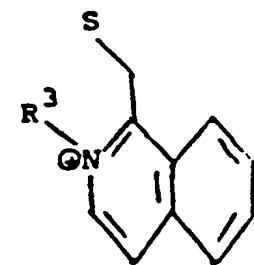
15



20



25



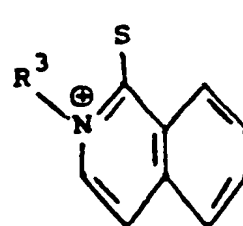
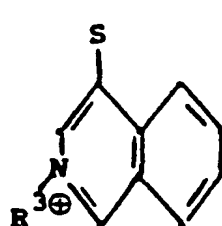
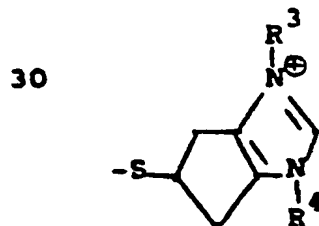
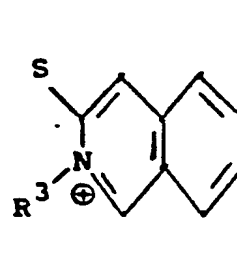
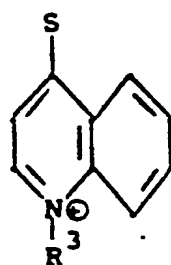
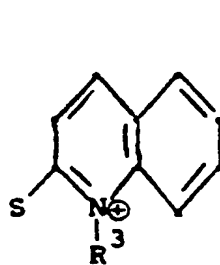
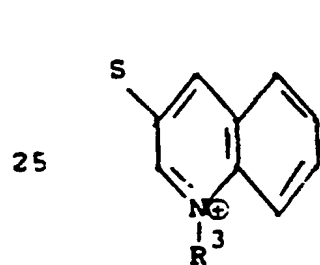
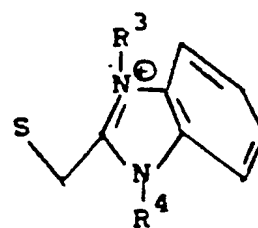
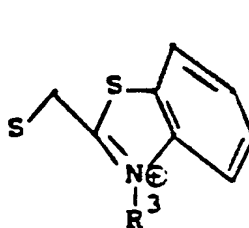
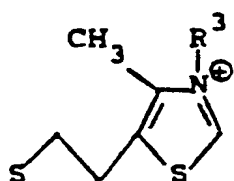
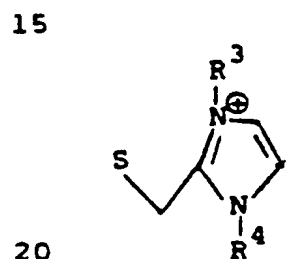
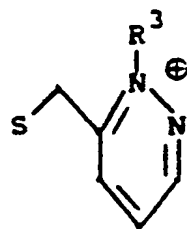
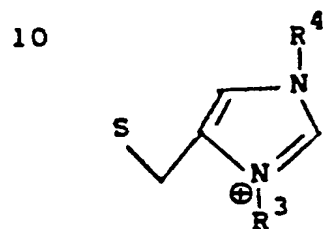
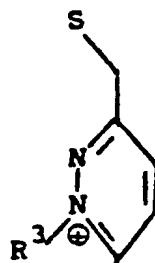
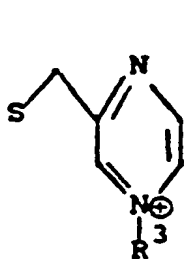
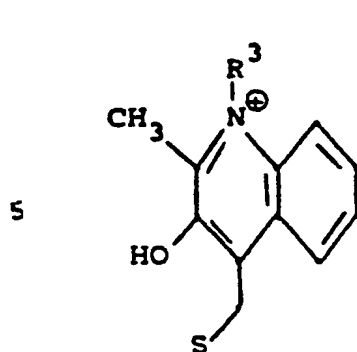
30

2360P/0840A

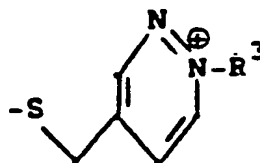
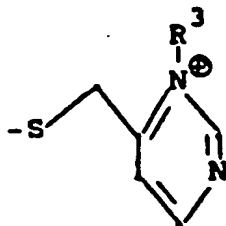
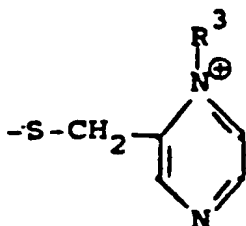
2361P/0840A

-17-

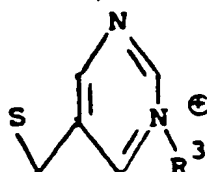
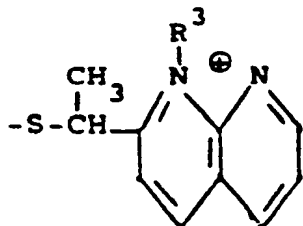
16622IH



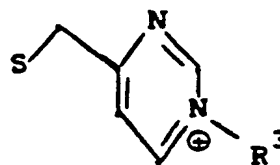
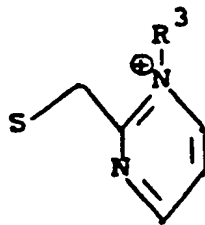
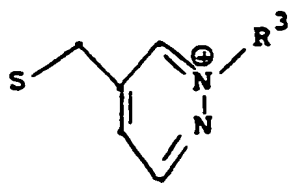
5



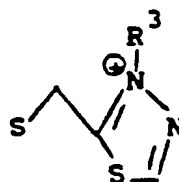
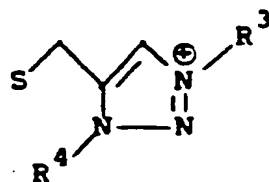
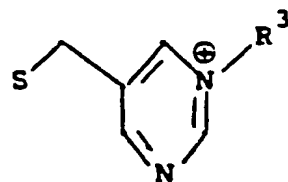
10



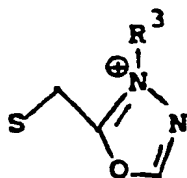
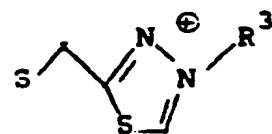
15



20




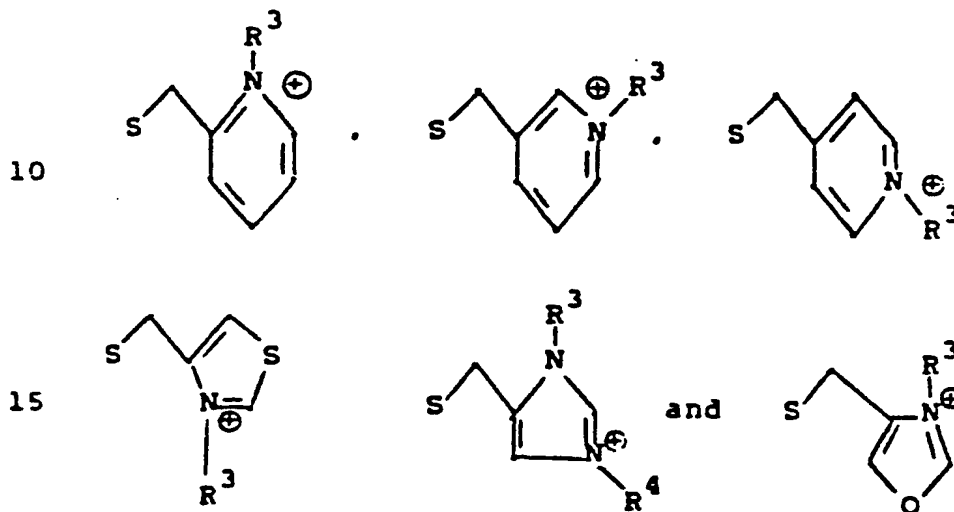
25



and the like.

30

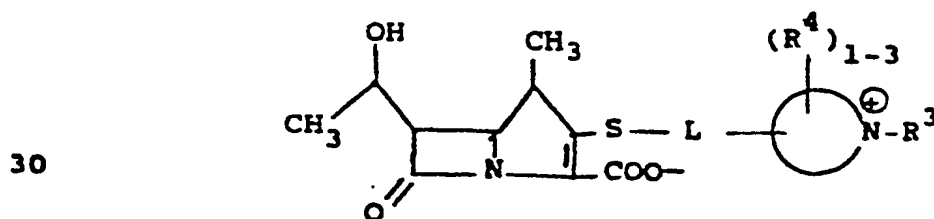
A preferred S-L--R³ group is monocyclic heteroaryl having 5-6 ring atoms and optionally one heteroatom additional to the N atom already present, e.g.,



where R³ and R⁴ are as defined in the preferred list above.

A more preferred subclass includes the nuclei shown above where R³ is CH₃ and R⁴ is CH₃.

The compounds of Formula I include inner (Zwitterion) salts when Y is COO⁻ e.g.



2360P/0840A

2361P/0840A

-20-

16622IH

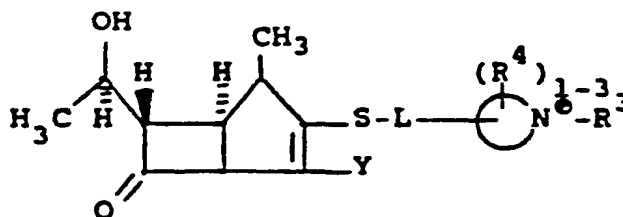
or, when Y is other than COO^\ominus , salts with an external, physiologically acceptable counterion z^\ominus such as Cl^\ominus , Br^\ominus , I^\ominus , OCH_3^\ominus , $\text{OSO}_2\text{CP}_3^-$, $\text{OP}(\text{O})(\text{O phenyl})_2^\ominus$ and the like.

5 The inner salts are preferred.

Again, the compounds of Formula I include the stereoisomers as mixtures and as separate isomers.

A preferred isomer configuration is:

10



15

Ia

The compounds of the present invention (i) are valuable antibiotics active against various Gram-positive and Gram-negative bacteria and accordingly find utility in human and veterinary medicine. Representative pathogens which are sensitive to antibiotics I include: Staphylococcus aureus, Escherichia coli, Klebsiella Pneumoniae, Bacillus subtilis, Salmonella typhosa, Pseudomonas and Bacterium proteus. The antibacterials of the invention are not limited to utility as medicaments; they may be used in all manner of industry, for example: additives to animal feed, preservation of food, disinfectants, and in other industrial systems where control of bacterial growth is desired. For example, they may be employed in aqueous compositions in concentrations ranging from 0.1 to 100 parts of

2360P/0840A

2361P/0840A

-21-

16622IH

antibiotic per million parts of solution in order to destroy or inhibit the growth of harmful bacteria on medical and dental equipment and as bactericides in industrial applications, for example in waterbased
5 paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

The compounds of this invention may be used in any of a variety of pharmaceutical preparations. They may be employed in capsule, powder form, in
10 liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically or parenterally by injection (intravenously or intramuscularly).

Compositions for injection, a preferred
15 route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents. Alternatively,
20 the active ingredient may be in powder form for reconstitution, at the time of delivery, with a suitable vehicle, such as sterile water. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions,
25 paints, or powders.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated as well as the route and frequency of administration -- the parenteral route
30 by injection being preferred for generalized infections. Such matters, however, are left to the routine discretion of the therapist according to

principles of treatment well known in the antibiotic art. In general, a daily dosage consists of from about 5 to about 600 mg of active ingredient per kg of body weight of the subject in one or more treatments per day. A preferred daily dosage for adult humans lies in the range of from about 10 to 240 mg of active ingredient per kg of body weight. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the chosen species of this invention (I).

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from 0.1% to 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 1500 mg of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 250 mg to 1000 mg. In parenteral administration, the unit dosage is usually the pure compound I in sterile water solution or in the form of a soluble powder intended for solution.

The preferred method of administration of the formula I antibiotic is parenteral by i.v. infusion, i.v. bolus, or i.m. injection.

For adults, 5-50 mg of Formula I antibiotic per kg of body weight given 2, 3, or 4 times per day is preferred. Preferred dosage is 250 mg to 1000 mg of the Formula I antibiotic given two (b.i.d.) three (t.i.d.) or four (q.i.d.) times per day. More specifically, for mild infections, and particularly

2360P/0840A

2361P/0840A

-23-

16622IH

urinary tract infections, a dose of 250 mg t.i.d. or q.i.d. is recommended. For moderate infections against highly susceptible gram positive and gram negative organisms, a dose of 500 mg t.i.d. or q.i.d. is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of 1000 t.i.d. or q.i.d. is recommended.

For children, a dose of 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg t.i.d. or q.i.d. is usually recommended.

Antibiotic compounds of Formula I are of the broad class known as carbapenems or 1-carbade-thiopenems. Certain of these carbapenems are susceptible to attack by a renal enzyme known as dehydropeptidase (DHP). This attack or degradation may reduce the efficacy of the carbapenem antibiotic. Inhibitors of DHP and their use with carbapenem antibiotics are disclosed in the prior art [see published European Patent Applications No. 79102616.4 filed July 24, 1979 (Patent Number 10573); 79102615.6, filed July 24, 1979 (application no. 15573); and No. 82107174.3, filed August 9, 1980 (application no. 72014)].

The present I compounds may, where DHP inhibition is desired or necessary, be combined or used with the appropriate DHP inhibitor as described in the aforesaid published applications. Thus, to the extent that the cited European patent applications 1.) define the procedure for determining DHP susceptibility of the present carbapenems and 2.)

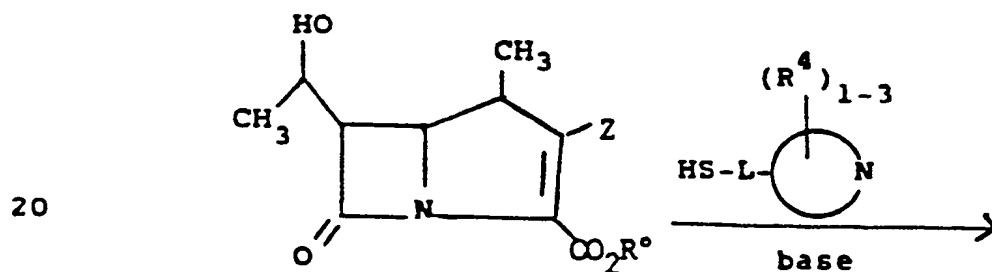
disclose suitable inhibitors, combination compositions and methods of treatment, they are incorporated herein by reference. A preferred weight ratio of I compound:DHP inhibitor in the combination compositions is about 1:1. A preferred DHP inhibitor is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid or a useful salt thereof.

These combination compositions and their use is another embodiment of the present invention.

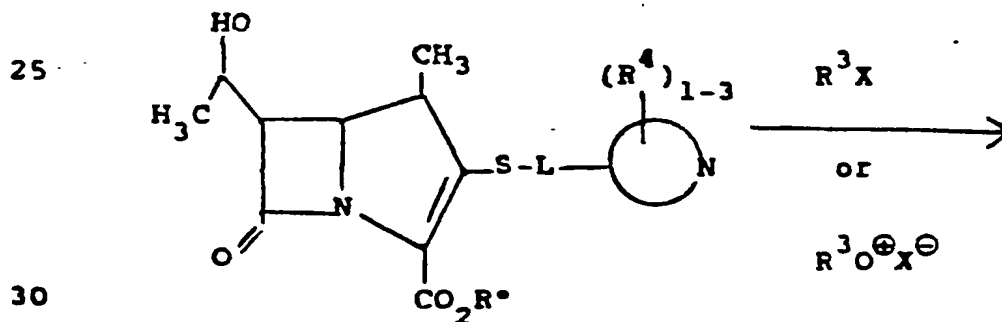
The compounds of Formula I may be prepared by any convenient process.

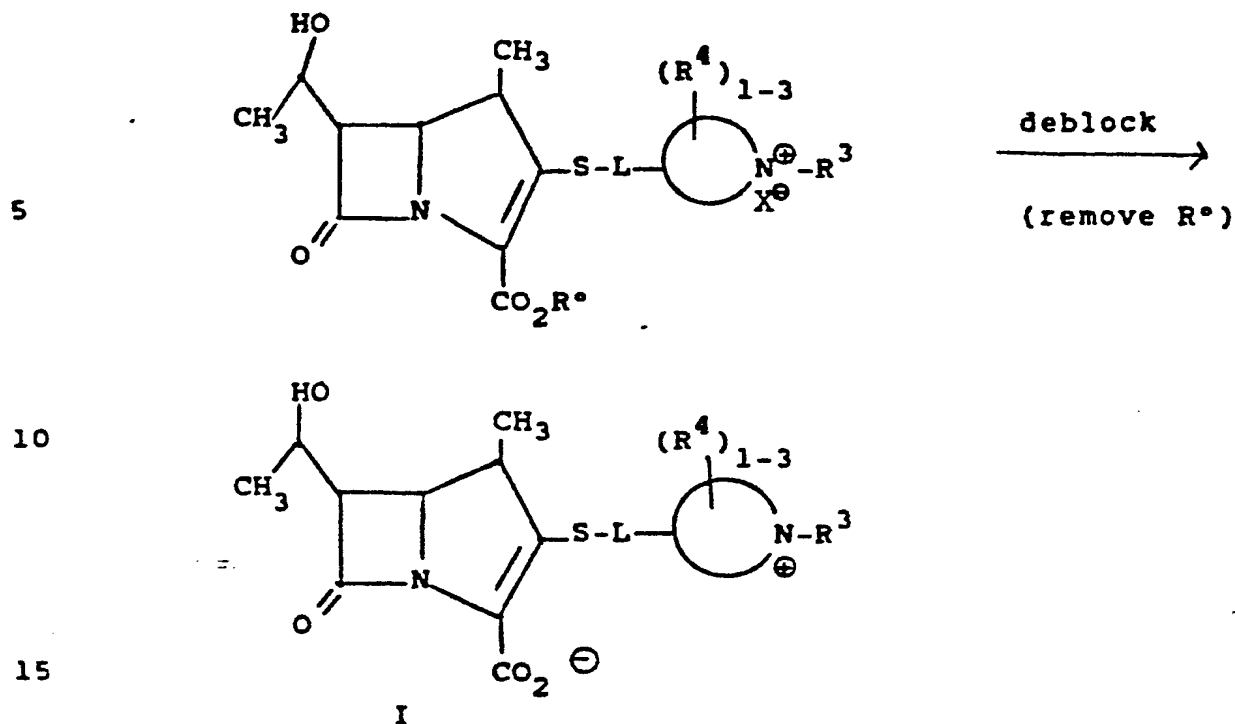
A. One such process is illustrated in the following reaction equations:

15

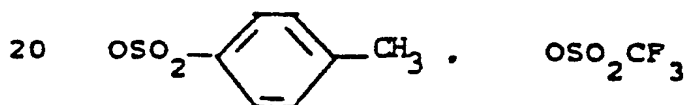


25

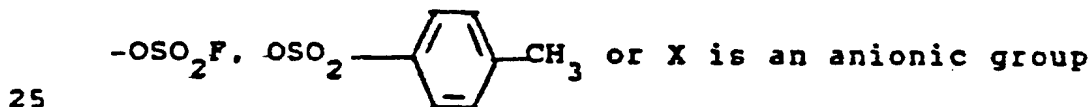




wherein Z is a leaving group such as $-\text{OPO}(\text{O})_2$.



and the like, X is a leaving group such as Br, I, OSO_2CF_3 ,



such as BF_4^- , SbF_6^- , PF_6^- and the like; and R^* is a protecting group such as p-nitrobenzyl or allyl. R^3 , L and R^4 are as defined above.

30 The side chain addition reaction is carried out in a solvent such as acetonitrile, dimethylformamide, dimethylacetamide or N-ethylpyrrolidinone in the presence of a base such as

2360P/0840A

16622IH

2361P/0840A

-26-

N,N-diisopropylethylamine, triethylamine or 4-dimethylaminopyridine at a temperature of from -40°C to 25°C for a period of five minutes to ten hours. The alkylation reaction is conducted in a solvent such as dichloromethane, dimethylformamide, acetonitrile or dimethylacetamide at a temperature of from -20°C to 25°C for a period of 1 to 24 hours. The deblocking reaction wherein R^o is p-nitrobenzyl is usually conducted in an aqueous system containing cosolvents such as tetrahydrofuran, ethanol, n-butanol, i-amyl alcohol, or ethyl acetate and a pH 6.8 to 7.0 aqueous buffer. Suitable buffers include phosphate buffers and buffers derived from non-nucleophilic amines such as N-methylmorpholine or morpholinopropane sulfonic acid. The reaction is conducted at 0°C to 40°C for 0.5 to 5 hours under 1-100 atmospheres of hydrogen in the presence of a catalyst such as 10% palladium on carbon or 20% palladium hydroxide on carbon. The final products are purified by ion exchange chromatography and/or reverse phase chromatography. When a pharmaceutically acceptable ester of the final product is desired, the deblocking step is omitted and the appropriate R^o group is incorporated into the starting material.

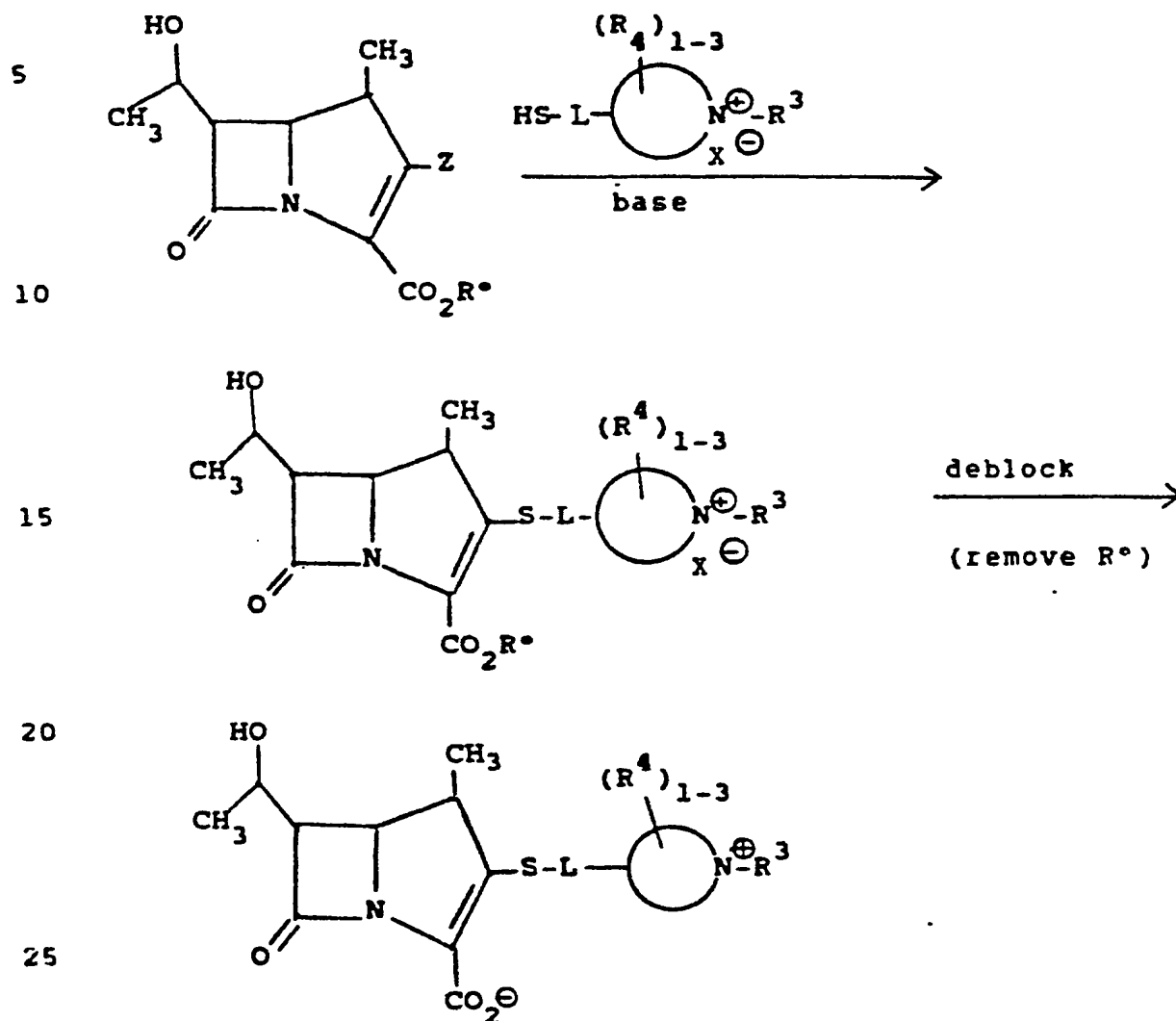
2360P/0840A

2361P/0840A

-27-

16622IH

B. A second process is illustrated by the following set of equations:



wherein Z, X, L, R° , R^3 and R^4 are as defined above.

30 The difference between the above process and that earlier described is that the side chain moiety is alkylated with the group R^3 prior to addition to the carbapenem nucleus. The side chain addition step and deblocking are conducted as described above.

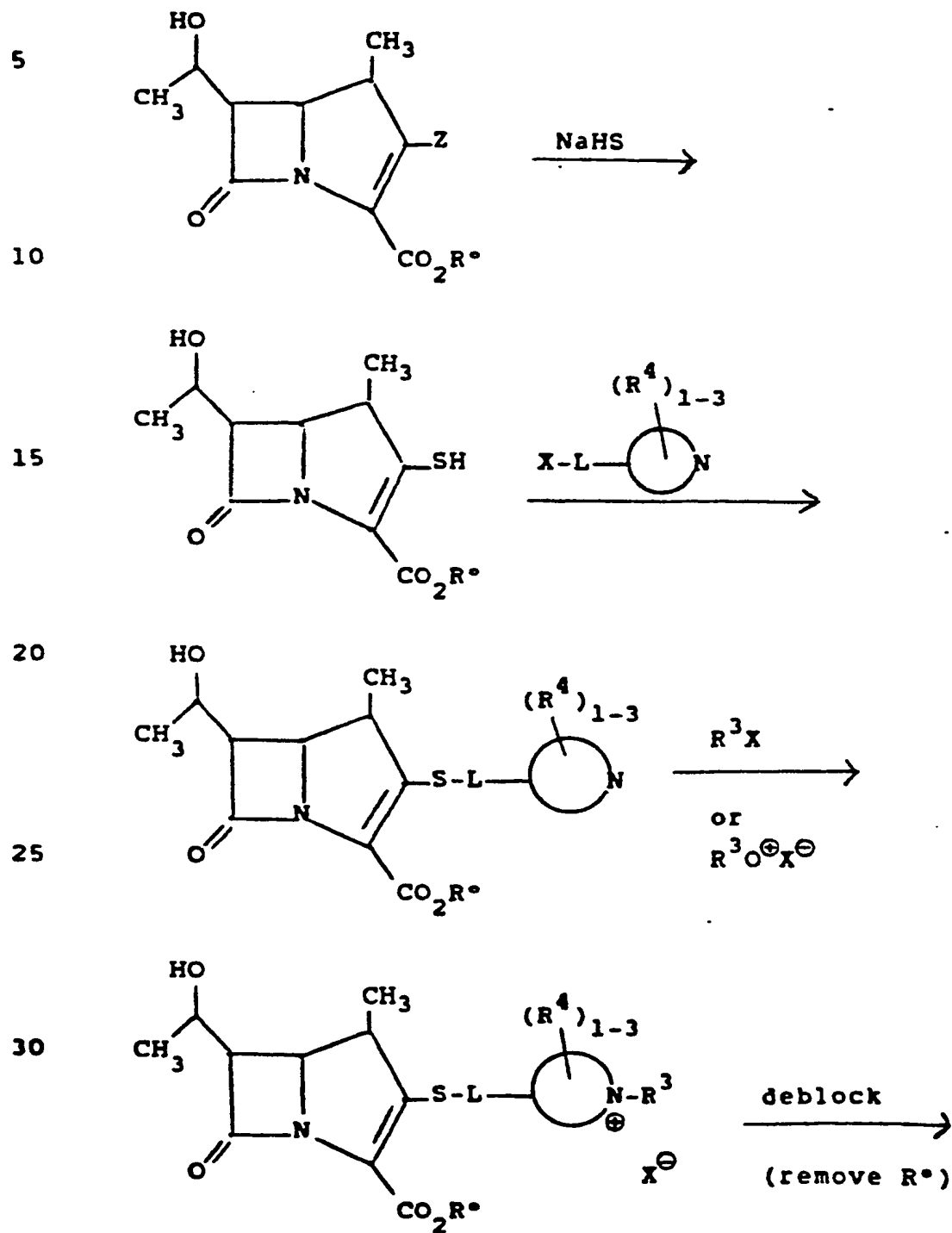
2360P/0840A

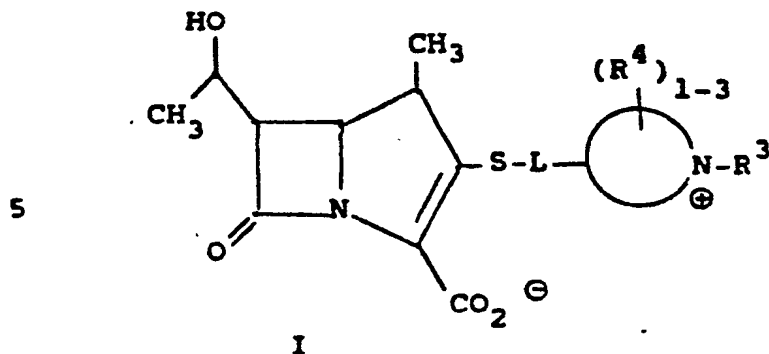
2361P/0840A

-28-

16622IH

C. A third process is illustrated by the following set of equations:





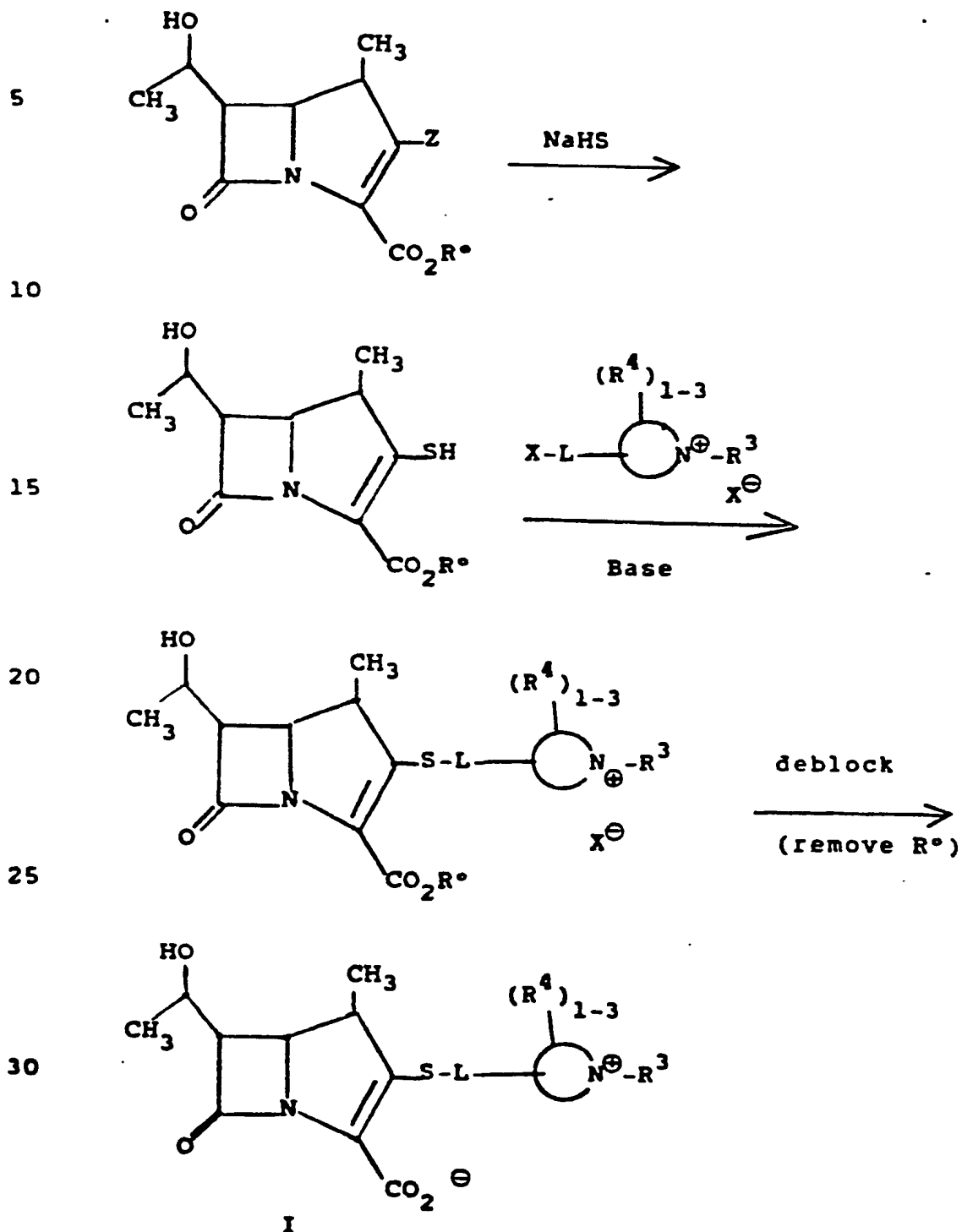
10 wherein Z, X, L, R^{*}, R³ and R⁴ are as previously defined.

In this case the 2-mercapto intermediate is generated from the activated carbapenem upon exposure to sodium hydrosulfide in dimethylformamide or dimethylacetamide at a temperature of from -50°C to -20°C for a period of five minutes to one hour. The sulfur atom is alkylated in a solvent such as acetonitrile, dimethylformamide, dimethylacetamide or the like in the presence of a base such as

20 N,N-diisopropylethylamine, triethylamine, 4-dimethylaminopyridine or the like at a temperature of from -40°C to 25°C for a period of from ten minutes to eight hours. The side chain alkylation, removal of R^{*} and purification of I is conducted as

25 described above.

D. A fourth process is illustrated by the following set of equations:



wherein Z, X, R⁰, R³, and R⁴ are as previously defined.

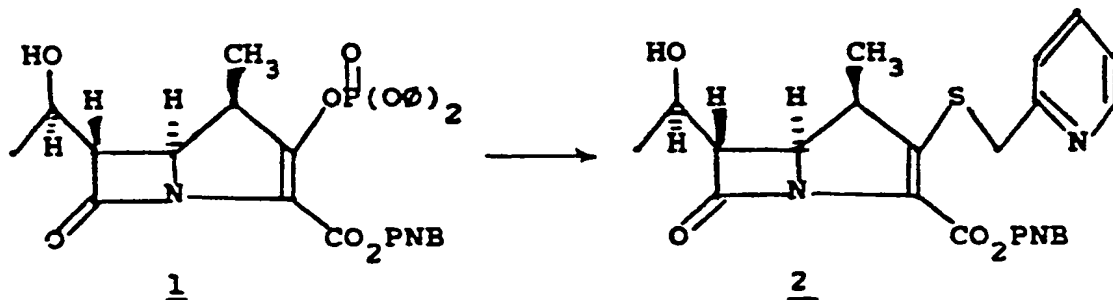
5 The difference between this process and that described in process C is that the side chain moiety is alkylated with the group R³ prior to addition to the carbapenem nucleus. The side chain addition step and the deblocking are conducted as described above.

10 The following examples illustrate the preparation of compounds of Formula I. The temperature is in degrees Celsius unless otherwise indicated.

EXAMPLE 1Step A.

5

10



15

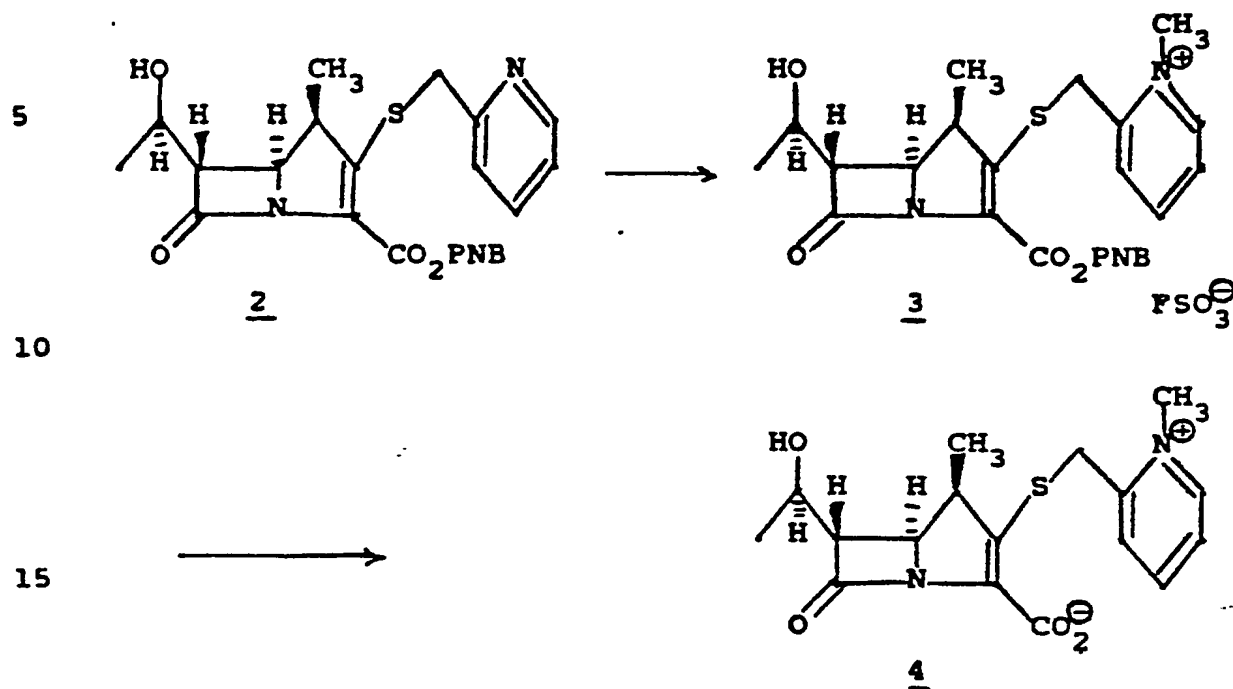
Preparation of p-Nitrobenzyl 1R,5S,6S-6-(1-1R-hydroxyethyl)-1-methyl-2-(2-pyridylmethylthio)-carbapen-2-em carboxylate

20

25

30

To a suspension of vinylphosphate (399 mg, 0.672 mmol) in 3 ml dry acetonitrile is added 127 μ l (0.732 mmol) of N,N-diisopropylethylamine and 94.7 μ l (0.84 mmol) of 2-pyridylmethyl mercaptan while the temperature is maintained at 0°. After stirring 3 hours at 0° the resulting homogenous solution is diluted with ethyl acetate and washed with 3 x 15 ml of 5% aqueous sodium bicarbonate. The organic phase is dried over sodium sulfate and concentrated to crude product in vacuo which is purified by preparative layer chromatography (R_f =0.14 in 9:1 ethyl acetate/hexanes). The desired ester 2 is obtained as a yellow foam (235 mg). nmr δ (CDCl_3): 1.22 (d), 1.31 (d), 3.22 (q), 3.73 (qt), 4.04 (d), 4.12 (q), 4.24 (d), 5.17 (d), 7.1-8.6 (m).

Step B.

Preparation of 1R,5S,6S-6-(1-1R-Hydroxyethyl-1-methyl-2-(2-N-methylpyridiniummethylthio)carbapen-2-em carboxylate

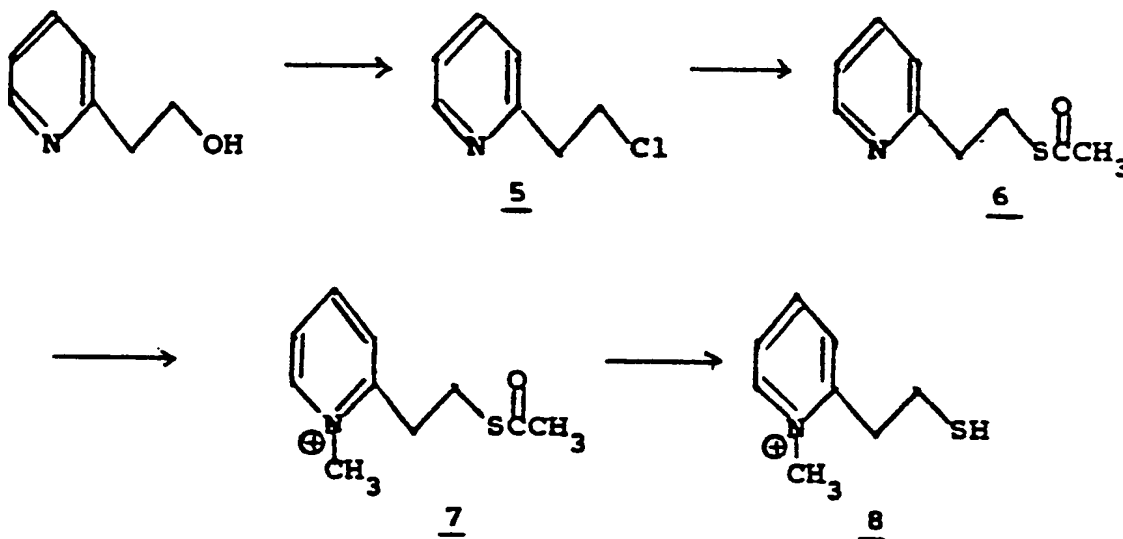
To a solution of 105.3 mg (0.224 mmol) ester 2 in 1.0 ml dichloromethane is added 20 μ l (0.246 mmol) of methyl fluorosulfonate. The mixture is stirred 3.5 hours at room temperature and then the resulting white precipitate of 3 is collected by filtration. The crude salt is dissolved in a mixture of 4.4 ml water, 4.4 ml n-butanol, 2.2 ml ethyl acetate, 2.2 ml 0.5M N-methylmorpholine hydrochloride (pH 6.8) and 32.9 mg of 20% palladium hydroxide on carbon is added. The mixture is hydrogenated at 35 psi for 1.6 hours at then the organic and aqueous phases separated. The aqueous phase is filtered to

2366P/0382P

-34-

16622IH

remove catalyst, washed with ethyl acetate and concentrated to about 2 ml. Purification is effected by chromatography on Dowex 50x4 (Na^+) at 5° with elution with water. Fractions containing 4 by UV are pooled, concentrated then lyophilized to yield 14.6 mg, $\text{UV } \lambda_{\text{max}}^{\text{H}_2\text{O}}$ 295 nm. nmr (D_2O): δ 1.13 (d), 1.25 (d), 3.36 (m), 3.47 (q), 4.21 (m), 4.4 (s), 7.89 (m), 8.45 (t), 8.77 (d).

EXAMPLE 2Step A.

Preparation of 2-(N-Methyl-2-pyridinium)ethanethiol 8

2-B-Hydroxyethyl)pyridine (1.00 g, 8.12 mmol) is charged into a 25 ml round-bottom flask under nitrogen and cooled to 0°. Thionyl chloride (650 μ l, 8.93 mmol) is added in small portions over 10 minutes with some anhydrous ether (about 200 μ l) to facilitate stirring. When the addition is complete the bath is removed and the mixture stirred 17 hours at room temperature. The resulting suspension is triturated with ether and the remaining solid is partitioned between aqueous potassium carbonate and ether (75 ml). The aqueous layer is extracted twice more with 75 ml portions of ether and the combined organics are dried over magnesium sulfate and evaporated to 1.15 g of 5 as a pale yellow oil. nmr (CDCl_3): δ 3.25 (t), 3.94 (t), 7.24 (m), 7.67 (tt), 8.6 (dd).

Crude 5 (1.00 g, 7.06 mmol) and 0.968 g (847 mmol) of potassium thioacetate are dissolved in 11.6 ml N,N-dimethylformamide and heated to 80° for 1.3 hours. The solvent is then removed in vacuo and the residue is taken up in ethyl acetate, washed with water and brine, dried over magnesium sulfate and concentrated to a dark red oil 6 (1.00 g, 5.52 mmol). nmr (CDCl_3): δ 2.34 (s), 3.08 (t), 3.32 (t), 7.2 (m), 7.64 (tt), 8.58 (dd).

The crude thioester 6 (1.00 g, 5.52 mmol) is dissolved in 4.6 ml N,N-dimethylformamide and 3.45 (55.2 mmol) of methyl iodide is added. The mixture is allowed to age at room temperature for 17 hours then concentrated to a brown solid. Trituration with dichloromethane followed by filtration yields 1.31 g (4.06 mmol) of 7 as a brown solid. nmr (D_2O): δ 2.35 (s), 3.26-3.4 (m), 4.44 (s), 7.96 (m), 8.48 (t), 8.8 (d).

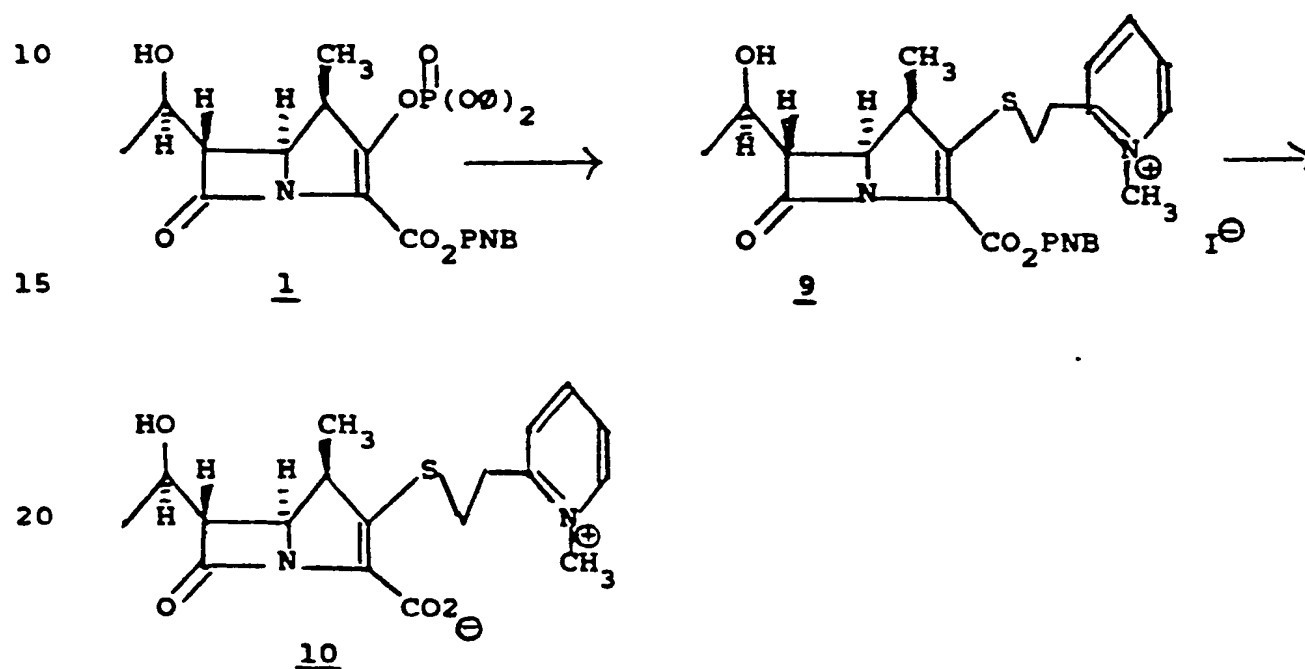
2366P/0382P

-36-

16622IH

A suspension of 100 mg (0.31 mmol) 7 in 590 μ l of 2N perchloric acid in methanol is stirred at room temperature for 18 hours. Pyridinium salt 8 is precipitated as a dark oil upon dilution of this mixture with anhydrous ether.

Step B.



25 Preparation of 1R,5S,6S-6-(1-1R-hydroxyethyl)-
1-methyl-2-(2-N-methylpyridinium-2-ethylthio)carba-
pen-2-em carboxylate

Vinylphosphate 1 (181 mg, 0.30 mmol) and
mercaptan 11 are combined in 1.26 ml of N,N-dimethyl-
30 acetamide and cooled to -20° . N,N-diisopropylethyl-
amine (106 μ l, 0.60 mmol) is added and the solution
aged to -20° for 35 minutes to give 9. The resulting
solution is transferred to a hydrogenation vessel

2366P/0382P

-37-

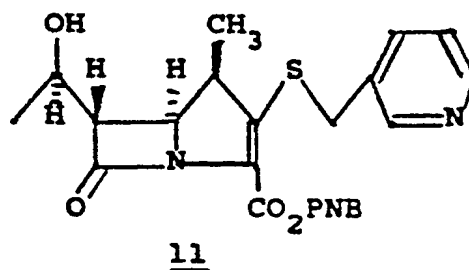
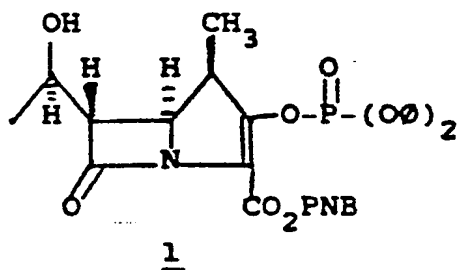
16622IH

with 5.86 ml isopropanol, 3 ml ethyl acetate, 5.86 ml water and 3.0 ml 0.1M pH 7 phosphate buffer. Palladium hydroxide (44 mg, 20% Pd) is added and the mixture hydrogenated to 41 psi for 2 hours. The resulting suspension is filtered to remove catalyst, diluted with ethyl acetate and worked up as in Example I to yield 2.9 mg of 10.

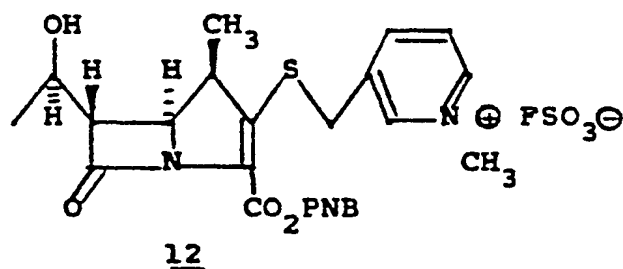
EXAMPLE 3

10

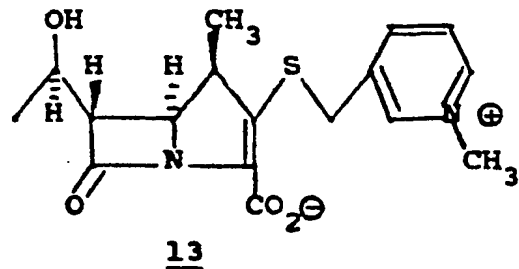
15



20



25



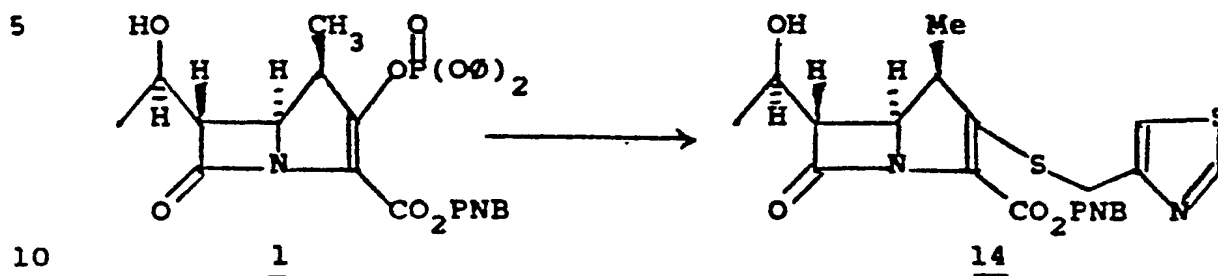
30

Preparation of 1R,5S,6S-6-(1-R-hydroxyethyl)-2-(3-N-methylpyridiniummethylthio)-1-methylcarbapen-2-em-3-carboxylate

Following the procedure in Example Ib,
5 above, the 8-methylvinylphosphate (1) (100 mg) is treated with 3-mercaptomethylpyridine (20.2 μ l) and diisopropylethylamine (32.5 μ l) in acetonitrile (0.5 ml). The product (11) is obtained crystalline from ethyl acetate yield 51 mg (65%).
10 To a suspension of 11 (47.8 mg) in methylene chloride (1 ml) is added methyl fluorosulfonate (9 μ l) at 0°. The solid changes during 10 minutes to a heavy oil. The methylene chloride is evaporated in a stream of nitrogen. The residue is hydrogenated in
15 THF-buffer solution and the product isolated via Dowex 50, Na⁺ chromatography to give 20 mg of the title compound 13. λ_{\max} 265 nm, E% 221, 296 nm, E% 221 (85% NH₂OH ext.). 200 MHz, NMR, δ 1.19 (d, J=7.5 Hz), 1.27 (d, J=6Hz), 3.3 (d, q, J=7.5 and 9
20 Hz), 3.46 (dd, J=2.8 and 6Hz), 4.14 (dd, J=2.8 and 9Hz), 4.24 (abq, J=15Hz and m (hidden)), 8.01 (dd, J=6 and 8.5 Hz), 8.51 (d, J=8.5 Hz), 8.69 (d, J=6Hz), 8.83 (s).

25

30

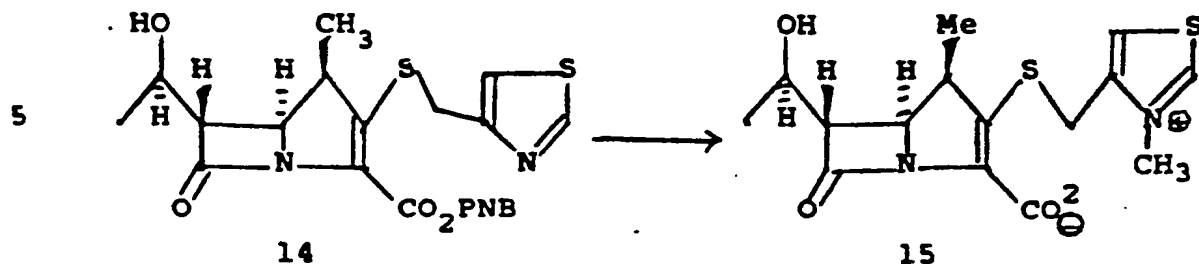
EXAMPLE 4Step A.

p-Nitrobenzyl(1R,5S,6S)-6-(1-R-hydroxyethyl)-2-(4-thiazolylmethylthio)-1-methylcarbapen-2-em-3-carboxylate 14

15 To an ice-cooled suspension of p-nitrobenzyl (1R,5S,6S)-6-(1-R-hydroxyethyl)-2-diphenylphosphoroxy-1-methylcarbapen-2-em 3-carboxylate (100 mg, 0.168 mmoles) in acetonitrile (0.5 ml) is added diisopropylethylamine (31 μ l, 0.179 mmoles) and 4-thiomethylthiazole (17 μ l, 0.17 mmoles). After 2 hours the mixture is diluted with methylene chloride, washed twice with pH 7 phosphate buffer, dried over anhydrous magnesium sulfate, evaporated and placed on a reverse phase-preparative tlc plate. 5% ethanol/chloroform

20

25 (R_f =0.5) the title compound 46 mg is isolated as a light yellow oil. 58% yield.

Step B.

10 1R,5S,6S-6-(1-R-hydroxyethyl)-2-(4-N-methylthiazolium-
methylthio)-1-methylcarbapen-2-em 3-carboxylate 18

p-Nitrobenzyl (1R,5S,6S)-6-(1-R-hydroxy-
 ethyl)-2-(4-thiazolylmethylthio)-1-methylcarbapen-2-em
 3-carboxylate 14 (0.04 g, 0.091 mmol) in aceto-
 15 nitrile (1.0 cc) is treated with methyl fluoro-
 sulfonate (8.0 μ l, 0.091 mmol) at room
 temperature for 2 hours. The solvent is evaporated
 by a stream of nitrogen and the residue is
 hydrogenated in THF-pH7 buffer solution. The
 20 isolation of the title compound is accomplished via
 Dowex 50 sodium cycle chromatography to give 10 mg of
 a powder 15.

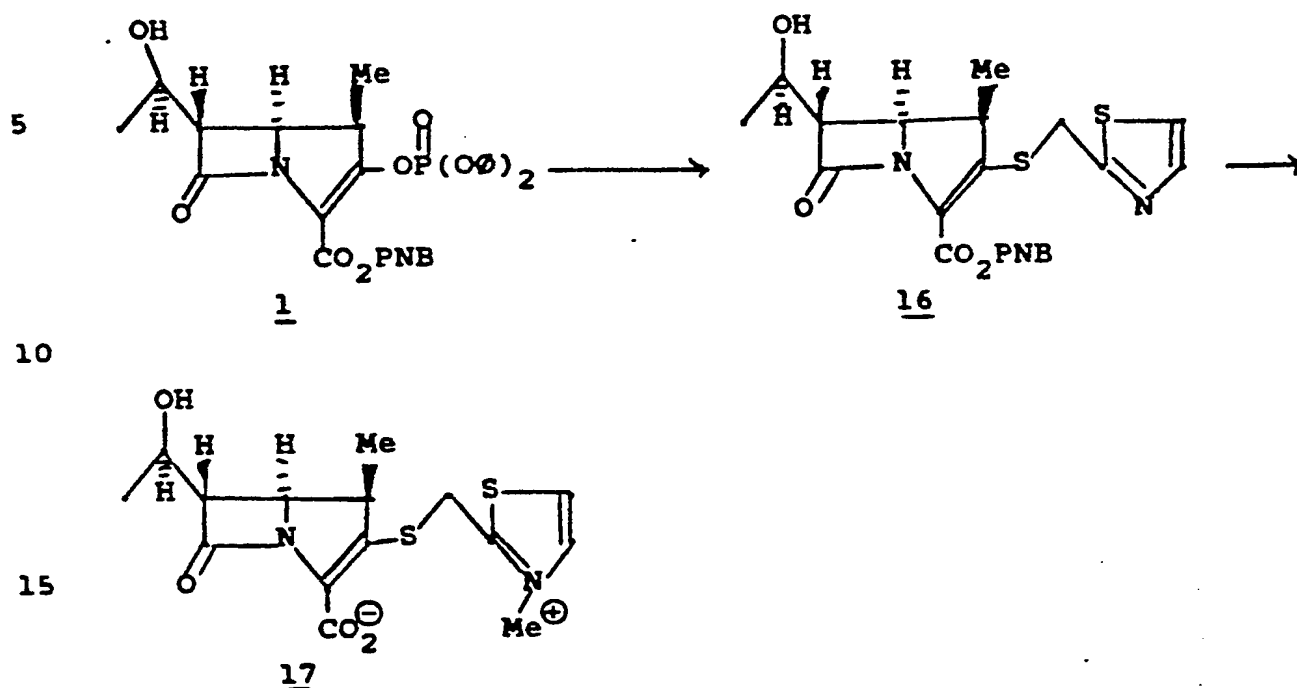
uv (H_2O) λ_{max} 295 nm

NMR (selected resonances) D_2O , δ 1.28 (3H, d,

25 J=6.5Hz), 3.48 (1H, dd, J=2.8, 6.0Hz), 1.18

\oplus

(3H, d, J=7.5Hz), N-methyl, 4.26 (3H, s).

EXAMPLE 5

20 1R,5S,6S-6-(1-R-hydroxyethyl)-2-(2-N-methylthiazolium-methylthio)-1-methylcarbapen-2-em 3-carboxylate 17

Following the procedures in Example IV, the β -methylvinylphosphate (1) (150 mg, 0.252 mmoles) is treated with 2-mercaptomethylthiazole (27 μ l, 0.316 mmoles) and diisopropylethylamine (55 μ l, 0.316 mmoles) in acetonitrile (1 cc). The product 16 is obtained as a colorless oil (82 mg) from a tlc plate. 71% yield.

To a suspension of 16 (0.05 g, 0.108 mmoles) in acetonitrile (1.5 cc) is added methyl fluoro-sulfonate (9.0 μ l, 0.108 mmoles). The solvent is evaporated by a stream of nitrogen and the residue is hydrogenated in THF- pH 7 phosphate buffer solution. The isolation of the title compound is accomplished via Dowex 50 sodium cycle chromatography to give 17 as 10 mg of a light yellow powder.

uv (H_2O) λ_{max} = 296 nm

NMR (selected resonances) (D_2O) δ 1.26 (3H, d, $J=6.5$ Hz), 3.45 (1H, dd, $J=2.8, 6.0$ Hz), 1.18

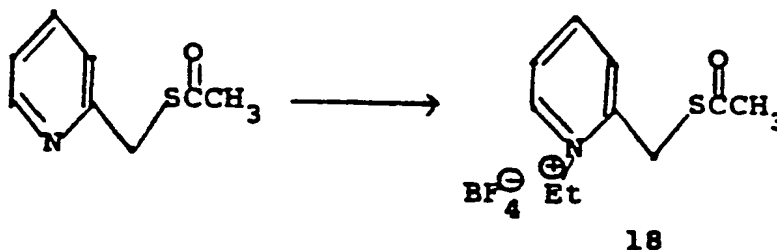
\oplus

5 (3H, d, $J=7.5$ Hz), N-methyl, 4.16 (3H, s).

EXAMPLE 6

Step A.

10

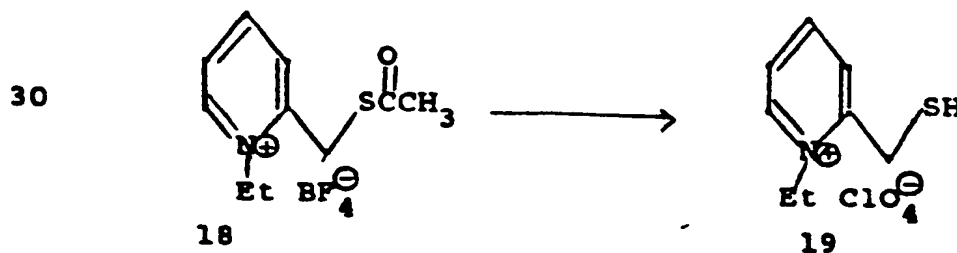


Preparation of N-Ethyl-2-pyridiniummethylthioacetate tetrafluoroborate 18

2-Picolyl thioacetate (200 mg) is treated with triethyloxonium tetrafluoroborate (227 mg) in methylene chloride (1 ml) at 0°C for 5 hours. The mixture is diluted with ether (20 ml) to separate product 18 as oil (210 mg). 60 MHz NMR ($CDCl_3$): δ 1.57 (t), 2.48 (s), 4.66 (s), 4.72 (q), 8.00-9.20 (m).

25

Step B.



2366P/0382P

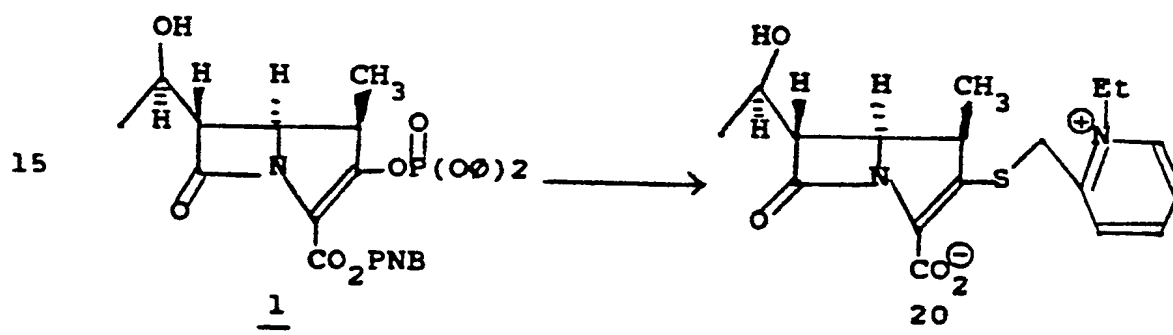
-43-

16622IH

Preparation of N-ethyl-2-pyridiniummethylmercapta-
perchlorate

Tetrafluoroborate salt 18 (210 mg) is treated with 2N HClO₄/methanol (1.54 ml) at room temperature for 2 days. The reaction mixture is then diluted with ether to separate oily product 19. 200 MHz NMR (DMSO-d₆): δ 1.55 (t), 4.64 (s), 4.70 (q), 8.00-9.18 (m).

10 Step C.



20 Preparation of 1R,5S,6S-6-(1-1R-hydroxyethyl)-2-(N-
ethyl-2-pyridiniummethylthio)-1-methylcarbapen-2-em
carboxylate

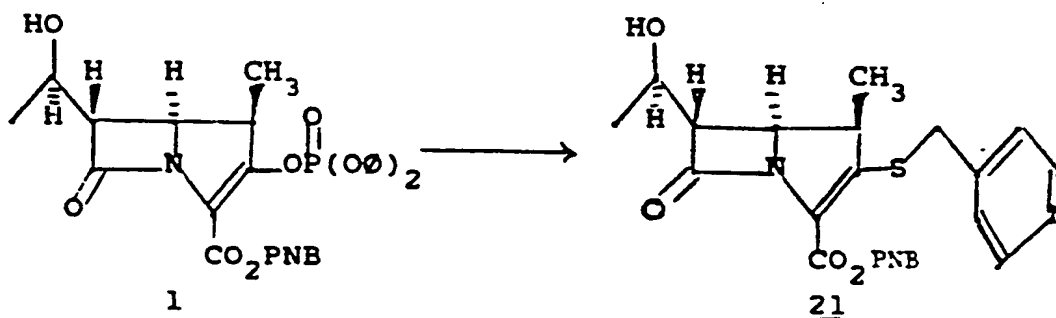
At -20°C, the 1-β-methylvinylphosphate I (100 mg) is treated with N-ethyl-2-pyridiniummethylmercaptan perchlorate 19 (70 mg) and diisopropylethylamine (66 μl) in N,N-dimethylacetamide (1 ml) for 20 minutes. The reaction mixture is then transferred into a hydrogenation flask which contains isopropanol (3.3 ml), 0.1M pH 7.0 phosphate buffer (3.3 ml) and 20% Pd/C (25 mg) and hydrogenated at 50 psi for 2 hours.

The mixture is filtered from catalyst, then diluted with ethyl acetate (20 ml) to separate

aqueous layer. The aqueous layer is charged to a Dowex-50x4 (Na^+) column which is eluted with D.I. water. The fractions containing product 23 are combined, concentrated, then lyophilized to give solid 20 (4.7 mg), $\text{uv } \lambda_{\text{max}}^{\text{H}_2\text{O}}$ 292 nm (NH_2OH extinguishable) and 268 nm, 200MHz NMR (D_2O): δ 1.21 (d), 1.33 (d), 1.70 (t), 3.45 (m), 3.55 (q), 4.30 (m), 4.82 (q), 7.9-8.95 (m).

EXAMPLE 7

Step A.



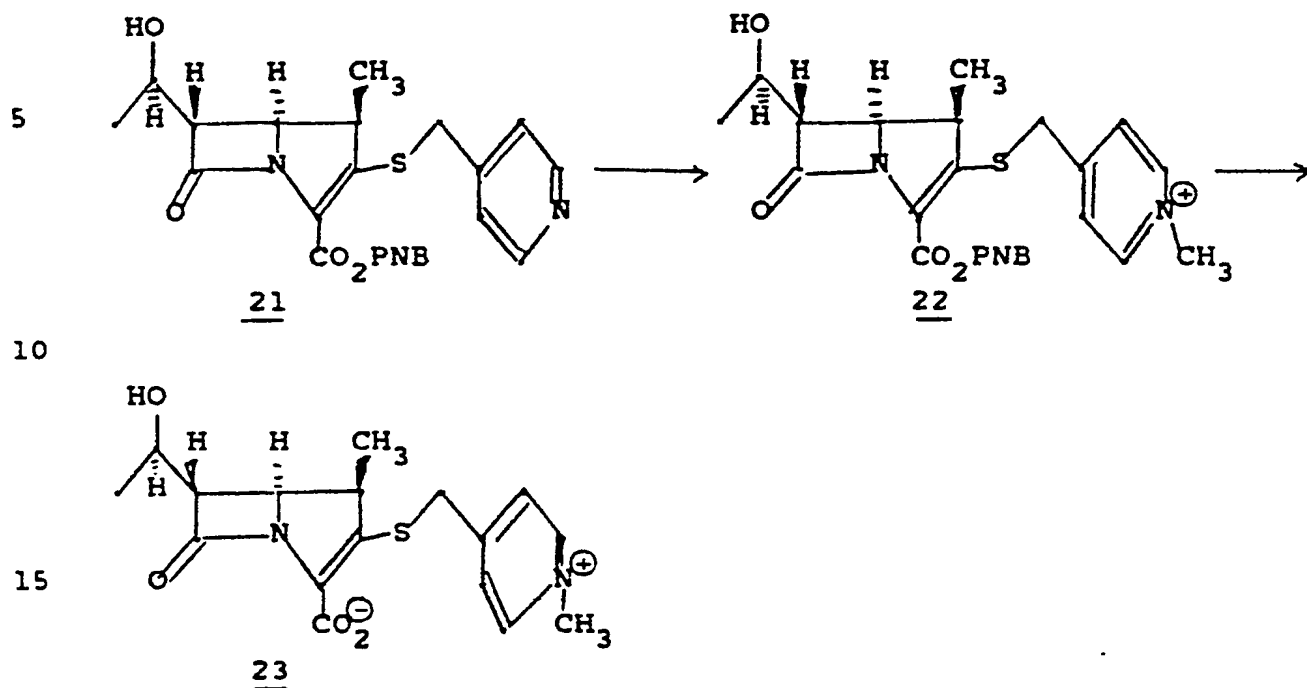
Preparation of p-Nitrobenzyl 1R,5S,6S-6-(1-1R-hydroxyethyl)-1-methyl-2-(4-pyridylmethylthio)carbapen-2-em carboxylate

Vinylphosphate 1 (225 mg, 0.378 mmol) and 4 pyridylmethanethiol hydrochloride (64 mg, 0.397 mmol) are dissolved/suspended in 1.8 ml acetonitrile and cooled to 0°. N,N-Diisopropylethylamine (145 μl , 0.832 mmol) is added and the resulting homogenous solution stirred 45 minutes. The mixture is diluted with ethylacetate, washed with aqueous bicarbonate and brine, dried over magnesium sulfate and evaporated to yield 202 mg of 21 as a yellow foam.

2366P/0382P

-45-

16622IH

Step B.

Preparation of 1R,5S,6S-6-(1-1R-hydroxyethyl)-1-methyl-2-(N-methyl-4-pyridiniummethylthio)carbapen-2-em carboxylate

Ester 21 (202 mg, 0.43 mmole) is dissolved in 2 ml dichloromethane and cooled to 0°. Methyl fluoro-sulfonate (38 µl, 0.473 mmol) is added resulting in an orange precipitate. After stirring 30 minutes at 0° the suspension is concentrated to yield crude 22 which is transferred to a hydrogenation vessel with 7.5 ml n-butanol, 3.8 ml ethyl acetate, 7.5 ml water and 3.8 ml of pH 6.8 0.5M N-methylmorpholine hydro-chloride buffer. Palladium hydroxide (20% on carbon, 57 mg) is added and the mixture hydrogenated at 45 psi for one hour. Workup and purification is conducted as in Example Ic, above, to yield 17 mg of 23.

uv (water): λ_{\max} 293 nm, NH_2OH extinguished
 λ_{\max} 294 nm.

NMR (D_2O). δ 1.19 (d, $J=7.2$ Hz, C_1 , CH_3). 1.27
(d, $J=6.3$ Hz, $\text{CH}(\text{OH})\text{CH}_3$). 3.29 (qd, $J=9.6$, 7.5 Hz,
5 H_1). 3.47 (dd, $J=6.0$, 2.8 Hz, H_6). 4.10 (dd,
 $J=9.6$, 2.8 Hz, H_5). 4.23 (quint, $J=6.3$ Hz, CHOH).
4.15 (d, $J=15.1$ Hz, $\text{SCH}_\text{A}\text{H}_\text{B}$). 4.35 (d, $J=15.1$ Hz,
 $\text{SCH}_\text{A}\text{H}_\text{B}$). 4.35 (s, N-CH_3). 7.99 (d, $J=6.7$ Hz,
10 ArH). 8.69 (d, $J=6.7$ Hz, ArH).

10

15

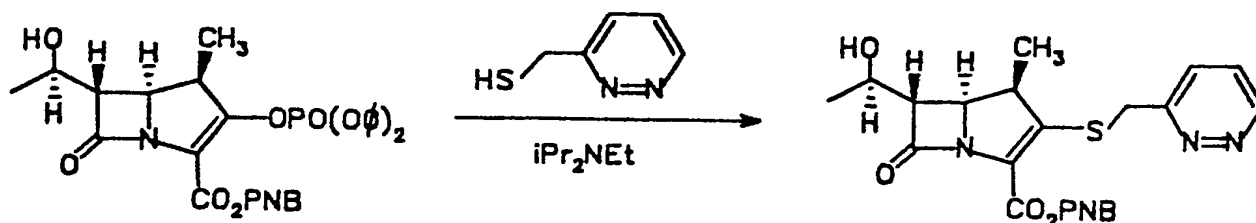
20

25

30

-47-

16622IH

EXAMPLE 8Step A:

p-Nitrobenzyl (1R,5S,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)-1-methylcarbapen-2-em 3-carboxylate

- A suspension of p-nitrobenzyl(1R,5S,6S)-2-(diphenylphosphono)oxy-6-[1(R)-hydroxyethyl]-1-methyl-carbapen-2-em 3-carboxylate (168 mg, 0.282 mmol) in anhydrous acetonitrile (2 cc) was cooled in an ice-bath under a nitrogen atmosphere and was treated with N,N-diisopropylethylamine (50 μ l, 0.282 mmol), followed by the dropwise addition of 3-mercapto-methylpyridazine* (35.6 mg, 0.282 mmol). The solid slowly dissolved and after 30 minutes the solution was diluted with methylene chloride, was washed with 0.1N pH 7 phosphate buffer, dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was chromatographed on a 1 mm x 20 cm x 20 cm silica gel GF plate, using 5% ethanol-methylene chloride as a developing solvent, to give the title compound (81 mg) as a white solid.
- mp 153°C (dec) Thomas Hoover Capillary Melting Point Apparatus (uncorrected)

IR (Nujol) β -lactam ν_{\max} 1740 cm^{-1}

NMR (CDCl_3) δ 1.27 (d, $J=6.5$ Hz, CH_2CHOH), 1.33
 (d, $J=7.5$ Hz, $\text{HC}-\text{CH}_3$), 3.29 (dd, $J=2.8, 6.5$ Hz,
 25 H6), 3.90 (dq, $J=7.5, 9.1$ Hz, H1), 4.12+4.56
 (ABq, $J=14.8$ Hz, SCH_2), 4.14 (dd, $J=2.8, 9.1$
 Hz, H5), 4.24 (P, $J=6.5$ Hz, CH_3CHOH), 5.20+5.50
 (ABq, $J=14.0$ Hz, CH_2Ar), 7.51 (dd, $J=5.0, 8.2$
 Hz, pyridazinyl H5), 7.66 (d, $J=8.6$ Hz,
 30 pyridazinyl H4), 7.66 (d, $J=8.8$ Hz, 2ArH), 8.24
 (d, $J=8.8$ Hz, 2ArH), 9.14 (d, $J=5.0$ Hz,
 pyridazinyl H6).

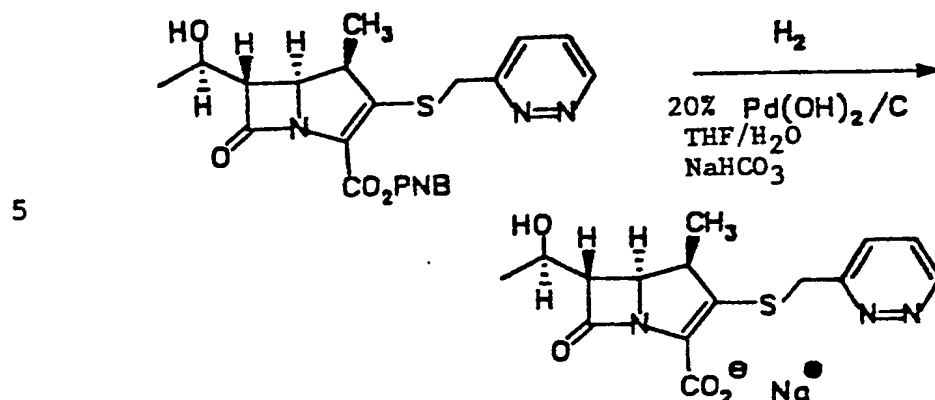
*

3-Mercaptomethylpyridazine

K. Yu. Novitsuii, N. K. Sadovaya, E. F.
 Kas'Yanova, L. K. Semna, Khimiya Geterotsiklicheskikh
 Soedinenii Vol 6, No. 3, pp 412-414 (1970).

-49-

16622IH

STEP B:

Sodium (1R,5S,6S)-6-[1(R)-hydroxyethyl]-2-[3-pyridazinylmethylthio]-1-methylcarbapen-2-em 3-carboxylate

A suspension of p-nitrobenzyl (1R,5S,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)-1-methylcarbapen-2-em 3-carboxylate (1.5 g, 0.0032 mol) in a mixture of water (0.1 L), containing sodium bicarbonate (0.27 g, 0.0032 mol), and tetrahydrofuran (0.1 L), was hydrogenated for 2 hours at 40 psig in the presence of 20% Pd(OH)₂/C (0.3 g). The mixture was filtered through Solka-Floc and the solution was washed with ethylether. The aqueous phase was concentrated under vacuum to ca. 50 ml and was freeze-dried giving (1.19 g) of the title compound as a light yellow solid.

IR (Nujol) β -lactam ν_{\max} 1740 cm⁻¹
 UV (H₂O) λ_{\max} 300 (ϵ 6,620) 83% H₂NOH extinguished

NMR (D₂O) δ (ppm) 1.14 (d, J=7.5 Hz, CHCH₃), 1.26 (d, J=6.5 Hz, CH₃CHOH), 3.40 (dd, J=2.6, 6.5 Hz, H₆), 3.40 (m, H₂), 4.04 (dd, J=2.6, 9.1 Hz, H₅), 4.20 (P, J=6.5 Hz, CH₃CHOH), 4.22+4.41 (AB₂, J=15.0 Hz, S-CH₂), 7.80 (dd, J=5.0, 7.3

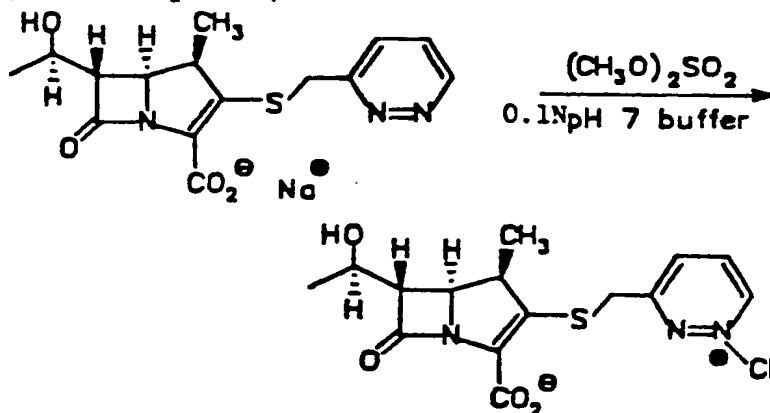
30

-50-

16622IH

STEP C:

Hz, pyridazinyl H5), 7.94 (dd, J=8.8, 1.5 Hz, pyridazinyl H4), 9.08 (dd, J=5.0, 1.1 Hz, pyridazinyl H6).



(1R,5S,6S)-6-(1(R)-Hydroxyethyl)-2-(1-methyl-3-pyridaziniummethylthio)-1-methylcarbapen-2-em 3-carboxylate

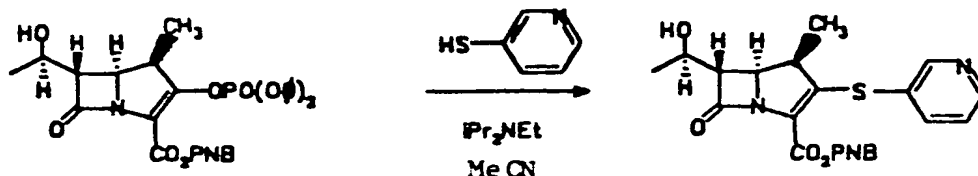
A solution of sodium (1R,5S,6S)-6-(1(R)-hydroxyethyl)-2-(3-pyridazinylmethylthio)-1-methylcarbapen-2-em 3-carboxylate (1.0 g, 0.0028 mol) in 0.1N pH 7 phosphate buffer (20 cc) was cooled in an ice-bath and treated with dimethylsulfate (1.3 ml, 0.014 mol). The mixture was stirred rapidly in the cold for 150 minutes, while incremental amounts of 1N NaOH were added in order to maintain a pH range of 6.8 to 7.2. The suspension was washed with ethylether and was loaded on a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 2.5 cm x 38 cm). The ice-cooled jacketed column was eluted with de-ionized water and 25 cc fractions were collected. Fractions 13-53 were combined, concentrated under vacuum to 50 cc and lyophilized to give the title compound (0.63 g) as a yellow solid.

-51-

IR (Nujol) β -lactam ν max 1750 cm^{-1}

UV (H_2O) λ max 290 ($\epsilon 7,050$) 78% H_2NOH
extinguished

5 NMR (D_2O) δ (ppm) 1.22 (d, $J=7.5\text{ Hz}$, CHCH_3), 1.28
(d, $J=6.5\text{ Hz}$, CH_3CHOH), 3.49 (dd, $J=3.0, 5.9$
Hz, H6), 3.55 (m, H1), 4.21 (dd, $J=2.8, 9.1\text{ Hz}$,
H5), 4.29+4.49 (ABq, $J=14.8\text{ Hz}$, S- CH_2), 4.64
(s, N- CH_3), 8.51 (dd, $J=5.0, 8.2\text{ Hz}$,
pyridazinyl H5), 8.57 (d, $J=8.8\text{ Hz}$, pyridazinyl
10 H4), 9.56 (d, $J=5.0\text{ Hz}$, pyridazinyl H6).

EXAMPLE 9Step A:

p-Nitrobenzyl (5S,6S)-6-[(1R)-hydroxyethyl]-2-(3-pyridylthio)-1(R)-methylcarbapen-2-em-3-carboxylate

A suspension of p-nitrobenzyl (5S,6S)-2-(diphenylphospheno)oxy-6-[(1R)-hydroxyethyl]-1(R)-methylcarbapen-2-em-3-carboxylate (446 mg, 0.75 mmol) in anhydrous acetonitrile (3 ml) was cooled to ca. -20°C under a nitrogen atmosphere and treated dropwise over 1 minute with a solution of 3-mercaptopyridine (108 mg, 0.97 mmol) in acetonitrile (1 ml) followed by N,N-diisopropylethylamine (169 μ l, 0.97 mmol). The resulting mixture was stirred for 2 hours at -20°C and for 1 hour at 0°C, then diluted with ethyl acetate, washed with brine, 5% aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to a pale yellow gum (406 mg). The crude product was chromatographed on EM silica gel 60 (10 g) using 1:1 ethyl acetate-methylene chloride as eluting solvent; 8 ml fractions were collected every 4 minutes. After 17 fractions, the eluting solvent was changed to ethyl acetate. Fractions 14-30 gave a pale yellow gum (306 mg) that crystallized from ethyl acetate-ethyl ether to afford the title compound (88 mg) as a white solid. The mother liquors gave additional product (39 mg) on standing at room temperature.

mp 109-111° (microhot stage);

IR (Nujol) ν_{\max} 1770, 1705, 1515, 1335 cm^{-1} ;

UV (dioxane) λ_{\max} 265 nm (ϵ 13,400), 323 nm (ϵ 16,520);

5 NMR (CDCl_3) δ 0.99 (d, $J=7.4$ Hz, CH_3CH), 1.32 (d, $J=6.2$ Hz, CH_3CHOH), 3.04 (dq, $J=9.6$ and 7.4 Hz, CH_3CH), 3.25 (dd, $J=2.7$ and 6.4 Hz, H6), 4.22 (dd, $J=2.7$ and 9.6 Hz, H5), 4.25 (dq, $J=6.4$ Hz, CH_3CHOH), 5.30 and 5.57 (two d, $J=13.8$ Hz, CH_2Ar), 7.35 (dd, $J=5.0$ and 7.8 Hz, pyridyl H5), 7.70 (d, $J=8.8$ Hz, 2ArH), 7.86 (ddd, $J=1.3$, 2.0 and 7.8 Hz, pyridyl H4), 8.25 (d, $J=8.8$ Hz, 2ArH), 8.64 (dd, $J=1.3$ and 5.0 Hz, pyridyl H6), 8.76 (d, $J=2.0$ Hz, pyridyl H2);

15 Mass Spectrum m/e 455 (M^+), 411, 369, 301, 111;

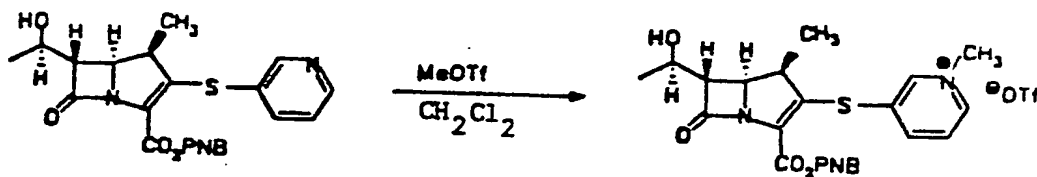
Anal. Calc'd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_6\text{S}$:

C, 58.02; H, 4.65; N, 9.23; S, 7.04

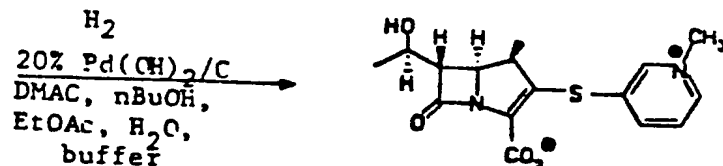
Found: C, 57.74; H, 4.64; N, 8.97; S, 6.84.

20

Step B:



25



30

-54-

(5S,6S)-6-[1(R)-Hydroxyethyl]-2-[(1-methyl-3-pyridinium)thio]-1(R)-methylcarbapen-2-em-3-carboxylate

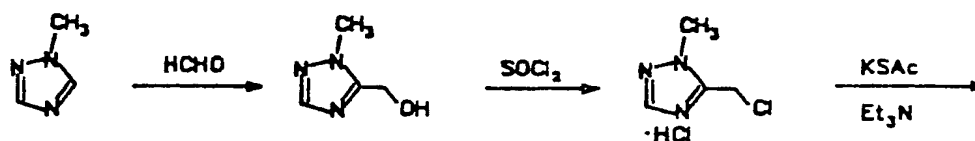
Methyl trifluoromethanesulfonate (17 μ l, 0.15 mmol) was added to an ice-cold, stirring solution of p-nitrobenzyl (5S,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridylthio)-1(R)-methylcarbapen-2-em-3-carboxylate (56.9 mg, 0.125 mmol) in anhydrous methylene chloride (1.25 ml), and the resulting mixture was stirred in the cold for 100 minutes. The solvent phase was decanted from the gummy precipitate which was washed with methylene chloride and dried under vacuum to a yellow foam. The foam was dissolved in N,N-dimethylacetamide (1 ml) and the solution was diluted with n-butanol (5 ml), ethyl acetate (2.5 ml), water (5 ml) and 0.5M pH 6.8 N-methylmorpholine hydrochloric acid buffer (2.5 ml), treated with 20% palladium hydroxide on carbon (25 mg), and hydrogenated at 45 psi for 90 minutes. The mixture was filtered through a celite pad using additional water. The aqueous portion of the filtrate was washed with methylene chloride and ether, then concentrated under vacuum to ca. 1 ml and added to a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 1.5 x 30 cm). The column was eluted with water in a cold room collected 170 drop fractions every 3.3 minutes. Fractions 10-16 were concentrated under vacuum to a few ml, filtered through a 0.45 μ CR acrodisc, and lyophilized to provide the title compound as a yellow, amorphous powder (24.3 mg).

-55-

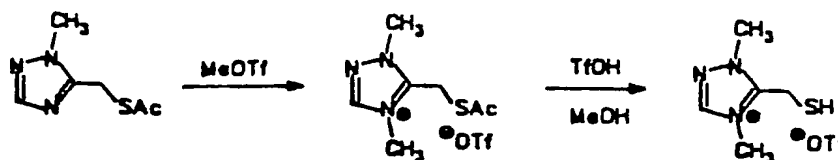
IR (Nujol) ν_{\max} 3350 (br), 1758, 1605 cm^{-1} ;
UV (0.05 pH 7.0 MOPS buffer) λ_{\max} 275 nm (sh,
 ϵ 7,610), 302 nm (ϵ 9,115);
UV (buffer + $\text{NH}_2\text{OH}\cdot\text{HCl}$) λ_{\max} 266.5 nm (ϵ 4,900),
5 319 nm (ϵ 2,010), extinguished λ_{\max} 301.5 nm
(ϵ ext. 7,480);

NMR (D_2O) δ 1.07 (d, $J=7.3$ Hz, CH_3CH), 1.27 (d,
 $J=6.4$ Hz, CH_3CHOH), 3.17 (dq, $J=9.8$ and 7.3 Hz,
 CH_3CH), 3.55 (dd, $J=2.9$ and 5.9 Hz, H6), 4.27
10 (dq, J 6.2 Hz, CH_3CHOH), 4.32 (dd, $J=2.9$ and
9.8 Hz, H5), 4.39 (s, NCH_3), 8.01 (dd, $J=6$ and
8 Hz, pyridyl H5), 8.58 (br d, $J=8$ Hz, pyridyl
H4), 8.71 (br d, $J=6$ Hz, pyridyl H6), 8.95 (br s,
pyridyl H2).

15

EXAMPLE 10Steps A - E:

20



1,4-Dimethyl-5-mercaptomethyl-1,2,4-triazolium
trifluoromethanesulfonate

Step A. 5-Hydroxymethyl-1-methyl-1,2,4-triazole

A solution of 1-methyl-1,2,4-triazole (4.16
5 g, 0.05 mol) in formalin (20 ml) was heated overnight
in a sealed tube at 135°C. After cooling, the
solvent was evaporated under vacuum to give a clear
liquid that partially solidified on standing. This
material was distilled to give a white, crystalline
10 solid (4.65 g) bp. ca. 110°C/0.25 mm. The solid
product was recrystallized from ethyl acetate-hexane
to afford the title compound (3.78 g, 67%) as white
crystals.

15 IR (Nujol) ν_{max} 3180, 1505, 1290, 1200, 1045,
1000 cm^{-1} ;

NMR (CDCl_3) δ 3.95 (s, CH_3), 4.75 (d, $J=6.5$ Hz,
 CH_2), 5.49 (t, $J=6.5$ Hz, OH), 7.78 (s, H5);

Anal. Calc'd for $\text{C}_4\text{H}_7\text{N}_3\text{O}$:

C, 42.47; H, 6.24; N, 37.15

20 Found: C, 42.67; H, 6.16; N, 37.35.

Step B. 5-Chloromethyl-1-methyl-1,2,4-triazole
hydrochloride

The hydroxymethyl triazole from Step 1 (1.00
25 g) was added to ice-cold thionyl chloride (4 ml) and
the resulting mixture was heated at reflux for 25
minutes. Excess thionyl chloride was evaporated
under vacuum. The solid residue was recrystallized
from ethanol-ethyl acetate to give the title compound
30 (1.17 g, 79% yield) as white crystals.

-57-

IR (Nujol) ν_{max} 1585, 1400, 1265, 1250, 960 cm^{-1} ;

NMR (D_2O) δ 4.07 (s, CH_3), 4.85 (s, HOD), 5.04
(s, CH_2), 8.53 (s, H5);

Anal. Calc'd for $\text{C}_4\text{H}_7\text{Cl}_2\text{N}_3$:

5 C, 28.59; H, 4.20; N, 25.01

Found: C, 28.73; H, 4.16; N, 25.00.

Step C. 5-Acetylthiomethyl-1-methyl-1,2,4-triazole

A mixture of the chloromethyltriazole from
10 Step 2 (609 mg, 3.63 mmol) and potassium thiolacetate
(497 mg, 4.36 mmol) in anhydrous acetonitrile (7.3
ml) was treated with a speck of dicyclohexano-18-
crown-6 and with triethylamine (531 μl , 3.81 mmol).
The resulting mixture was stirred at room temperature
15 for 3 hours. The mixture was filtered and the solids
washed with acetonitrile. The filtrate and washings
were evaporated under vacuum to a residue which was
trituated with three portions of ethyl acetate. The
ethyl acetate extracts were filtered, washed with
20 brine, dried over magnesium sulfate, filtered, and
evaporated under vacuum to afford the title compound
(526 mg, 85%) as an orange liquid.

NMR (CDCl_3) δ 2.40 (s, CH_3CO), 3.91 (s, CH_3),
4.26 (s, CH_2), 7.80 (s, H5).

25

Step D. 5-Acetylthiomethyl-1,4-dimethyl-1,2,4-tri-
azolium trifluoromethanesulfonate

A solution of 3-acetylthiomethyl-2-methyl-
1,2,4-triazole (244 mg, 1.43 mmol) in anhydrous
30 methylene chloride (1.4 ml) was cooled in an ice bath
under a nitrogen atmosphere and treated with methyl
trifluoromethanesulfonate (194 μl , 1.71 mmol). The

resulting mixture was stirred in the cold for 30 minutes, then evaporated under vacuum. The residue was triturated three times with diethyl ether, then dissolved in anhydrous methylene chloride and evaporated under vacuum to afford the title compound (484 mg, 100%) as a viscous orange oil.

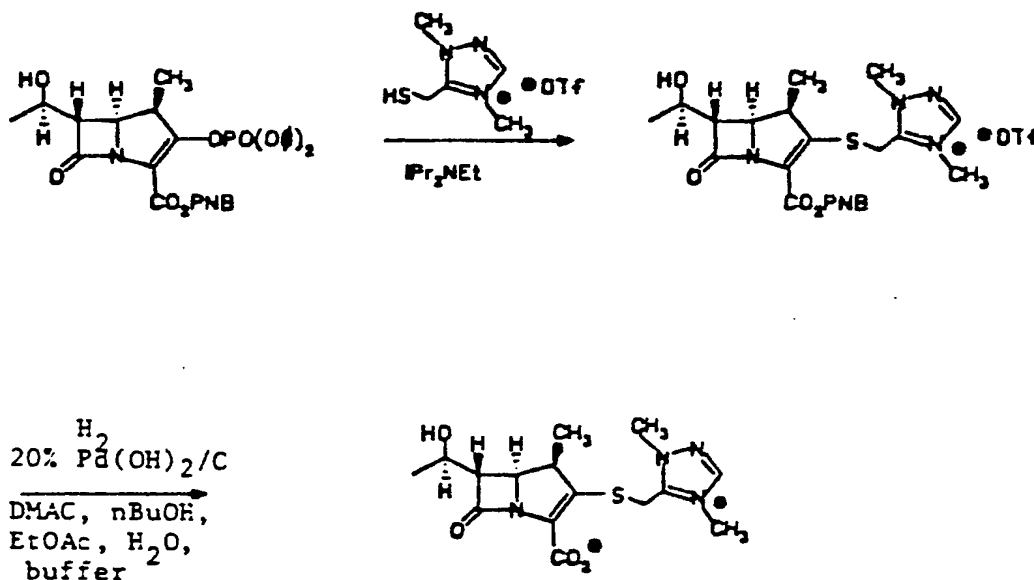
NMR (D_2O) δ 2.43 (s, CH_3CO), 3.95 (s, CH_3), 4.14 (s, CH_3), 4.62 (s, CH_2), 4.78 (s, HOD), 8.72 (s, H5).

Step E. 1,4-Dimethyl-5-mercaptomethyl-1,2,4-triazolium trifluoromethanesulfonate

A solution of the product from the preceding step (484 mg, 1.43 mmol) in anhydrous methanol (1.4 ml) was treated with trifluoromethanesulfonic acid (127 μ l, 1.43 mmol) and kept at room temperature for 18.5 hours. The solution was diluted with ethyl ether to precipitate the product as an oil. The oil was washed four times with ethyl ether, diluted with anhydrous methylene chloride, and evaporated under vacuum to provide the title compound (344 mg, 82%) as a pale orange oil.

NMR (D_2O) δ 3.93 (s, CH_3), 4.08 (s, CH_3), 4.25 (s, CH_2), 4.78 (s, HOD), 8.72 (s, H5).

16622IH

Step F:

(5S,6S)-2-(1,4-Dimethyl-1,2,4-triazol-5-ium)methylthio-6-[1(R)-hydroxyethyl]-1(R)-methylcarba-2-em-3-carboxylate

A solution of 1,4-dimethyl-5-mercaptopmethyl-1,2,4-triazolium trifluoromethanesulfonate (108 mg, 0.368 mmol) in anhydrous N,N-dimethylacetamide (2.3 ml) was cooled to -20°C under a nitrogen atmosphere and treated with p-nitrobenzyl (5S,6S)-2-(diphenylphosphono)oxy-6-[1(R)-hydroxyethyl]-1(R)-methylcarba-2-em-3-carboxylate (146 mg, 0.245 mmol) followed

by the dropwise addition over 6 minutes of a solution of N,N-diisopropylethylamine (64 μ l, 0.368 mmol) in dimethylacetamide (0.15 ml). The resulting solution was stirred at -20°C for 30 minutes, then diluted with n-butanol (12 ml), ethyl acetate (6 ml), water (12 ml), and 0.5M pH 6.8 N-methylmorpholine hydrochloric acid buffer (6 ml), treated with 20% palladium hydroxide on carbon (75 mg), and hydrogenated at 45 psi for 90 minutes. The mixture was filtered through a celite pad to remove the catalyst which was washed with water. The aqueous portion of the filtrate was washed with methylene chloride (3x) and ethyl ether, concentrated under vacuum to ca. 5 ml, and added to a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 1.5 x 33 cm). The column was eluted with water in a cold room, collecting 170 drop fractions. Fractions 7-12 were concentrated under vacuum to ca. 5 ml, filtered through a 0.45 μ CR acrodisc, and lyophilized to give the title compound (32.9 mg) as a white, amorphous powder.

IR (Nujol) ν_{max} 3400 (br), 1760, 1610, 1305 cm^{-1} ;

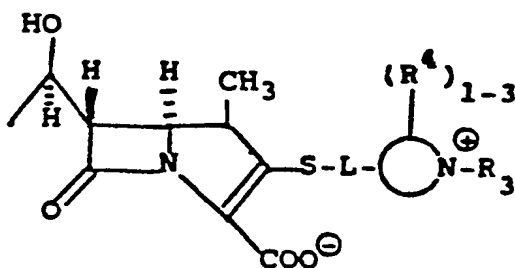
UV (0.05M pH 7.0 MOPS buffer) λ_{max} 294 nm (95% NH_2OH extinguished, $\epsilon_{\text{ext.}}$ 5,570);

NMR (D_2O) δ 1.19 (d, $J=7.2$ Hz, CH_3CH), 1.29 (d, $J=6.4$ Hz, CH_3CHOH), 3.42 (dq, $J=9.6$ and 7.2 Hz, CH_3CH), 3.57 (dd, $J=3.0$ and 5.8 Hz, H6), 3.94 (s, NCH_3), 4.09 (s, NCH_3), 4.28 (m, H5 and CH_3CHOH), 8.76 (s, triazolium H).

EXAMPLE 11

Utilizing the procedures of Examples 1-10,
the following compounds are prepared:

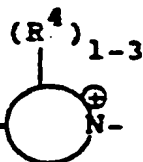
5



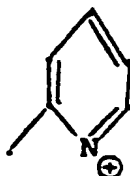
10

Com-
pound
No.

L

R³

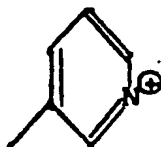
15

1 -CH₂-CH₂CH₂CH₃

20

2 -CH-
|
CH₂CH₃

"

CH₂CH₃3 -CH₂-CH₂CH₂CH₃

25

4 "

"

CH₂CH₃

30

5 "

CH₂CH₂CH₃

2360P/0840A

2361P/0840A

-62-

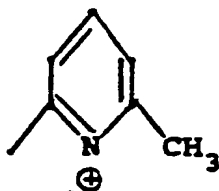
16622IH

6 -CH₂-

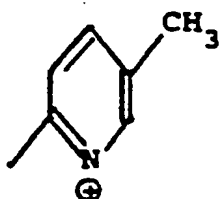
"

CH₂CH₃

5 7 "

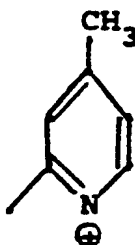
CH₃

10 8 "



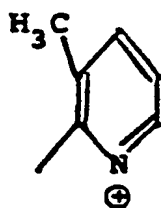
"

15 9 "



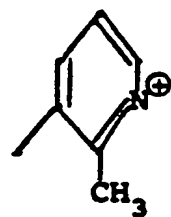
"

20 10 "



"

25 11 "



"

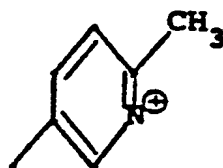
30 11 "

2360P/0840A

2361P/0840A

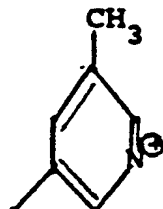
-63-

16622IH

12 -CH₂-CH₃

5

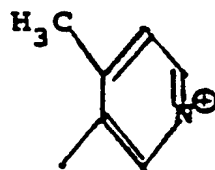
13 "



"

10

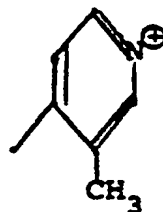
14 "



"

15

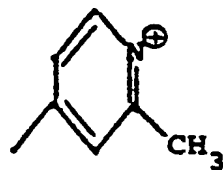
15 "



"

20

16 "



"

25

17 -CH₂CH₂-CH₂CH₃

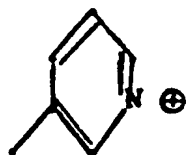
30

2360P/0840A

2361P/0840A

-64-

16622IH

18 -CH₂CH₂-CH₃

5

19 "



"

10

20 -CH-
CH₃

"

15

21 "



"

20

22 "



"

25

23 -CH₂-OCH₂

30

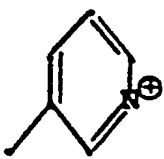

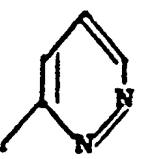
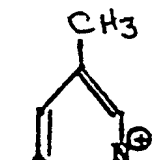
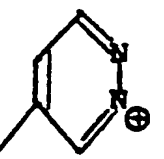
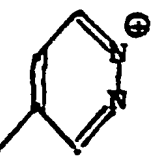
2360P/0840A

2361P/0840A

0170073

16622IH

-65-

24	-CH ₂ -		ØCH ₂ .
5			
25	"		"
10			
26	"		CH ₃
15			
27	"		"
20			
28	"		"
25			
29	"		"
30			

2360P/0840A
2361P/0840A

-66-

16622IH

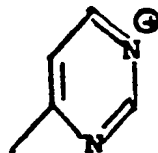
30 -CH₂-



CH₃

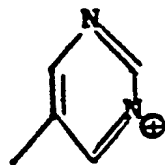
5

31 "



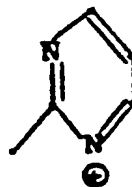
10

32 "



15

33 "



20

34 "



25

30 35 "



2360P/0840A

2361P/0840A

-67-

16622IH

36 -CH₂-CH₃

5



37 "

"

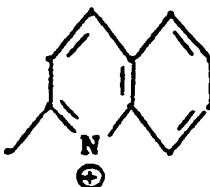
10



38 "

"

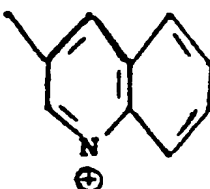
15



39 "

"

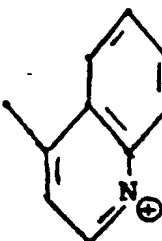
20



25 40 "

"

30



41 "

"



2360P/0840A

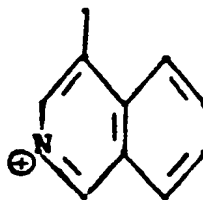
2361P/0840A

-68-

16622IH

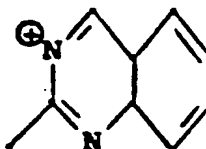
42 -CH₂-

5

CH₃

43 "

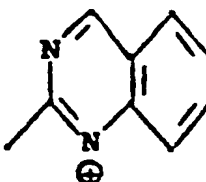
10



"

44 "

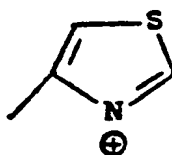
15



"

45 "

20

CH₂CH₂CH₃

46 "

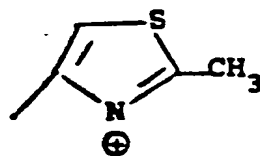
25

"

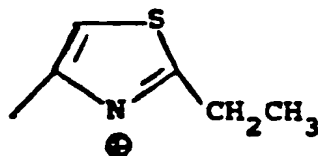
CH₂CH₃

47 "

30

CH₃

48 "



"

2360P/0840A

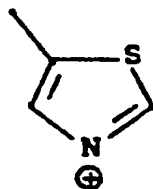
2361P/0840A

-69-

16622IH

49 -CH₂-

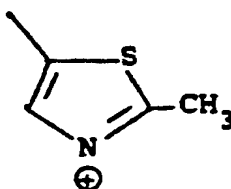
5



CH₃

50 "

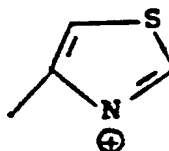
10



"

51 -CH-
CH₃

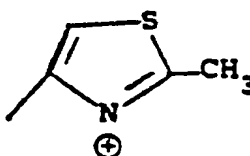
15



"

52 "

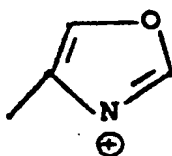
20



"

53 -CH₂-

25



"

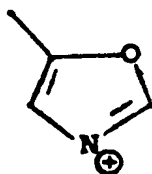
54 "

30

"

CH₂CH₃

55 "



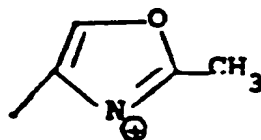
CH₃

2360P/0840A

2361P/0840A

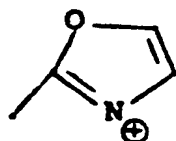
-70-

16622IH

56 -CH₂-CH₃

5

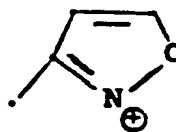
57 "



"

10

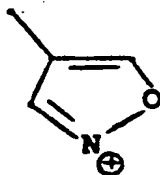
58 "



"

15

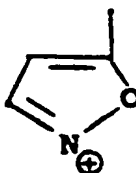
59 "



"

20

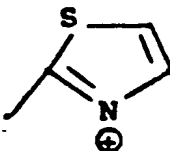
60 "



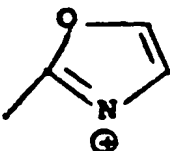
"

25

61 "

CH₂CH₃

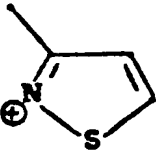
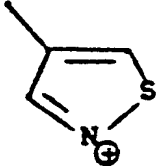
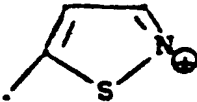
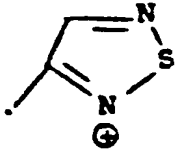
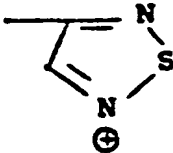
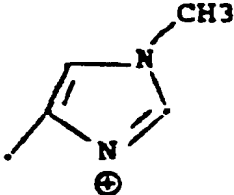
30

62 -CH₂CH₂-CH₃

2360P/0840A
2361P/0840A

-71-

16622IH

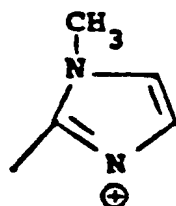
63	-CH ₂ -		CH ₃
5			
64	"		"
10			
65	"		"
15			
66	"		"
20			
67	"		"
25			
68	"		CH ₃
30			
69	"	"	-CH ₂ CH ₃

2360P/0840A

2361P/0840A

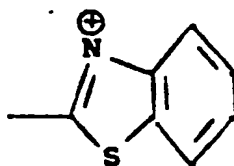
-72-

16622IH

70 -CH₂--CH₃.

5

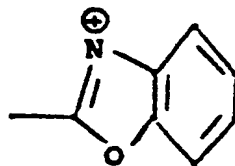
71 "



"

10

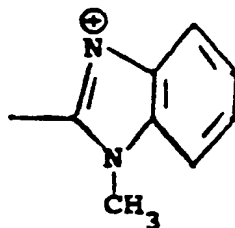
72 "



"

15

73 "



"

20

74 "

CH₂OCH₃

25

75 "

"

CH₂CN

30

76 "

"

CH₂CO₂H

77 "

"

CH₂SO₂CH₃

2360P/0840A

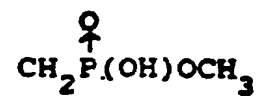
2361P/0840A

-73-

16622IH

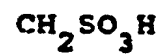
78 -CH₂-

"



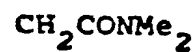
5 79 "

"



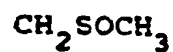
80 "

"



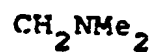
81 "

"



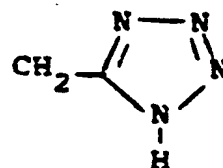
10 82 "

"



83 "

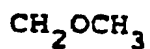
"



15

84 "

"

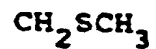


20



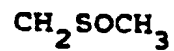
85 "

"



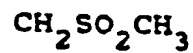
25 86 "

"



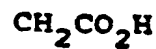
87 "

"



30 88 "

"



89 "

"




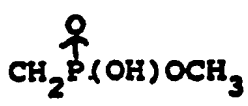
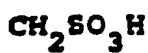
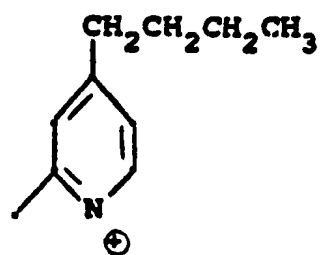

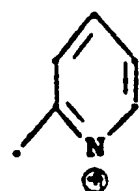

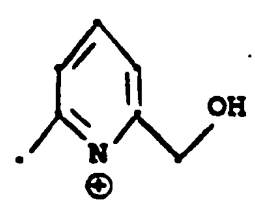
2360P/0840A

2361P/0840A

-74-

16622IH

	90	-CH ₂ -	"	$\text{CH}_2\overset{\text{O}}{\underset{\uparrow}{\text{P}}}(\text{OH})\text{OCH}_3$
5	91	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	92	"	"	CH_2CN
	93	"	"	CH_2NMe_2
10	94	"	"	$\text{CH}_2\text{CH}_2\text{NMe}_2$
15	95	"		CH_2OCH_3
	96	"	"	CH_2NMe_2
20	97	"	"	$\text{CH}_2\text{CH}_2\text{NMe}_2$
	98	"	"	CH_2CN
	99	"	"	CH_2SCH_3
25	100	"	"	CH_2SOCH_3
	101	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
30	102	"	"	$\text{CH}_2\text{CO}_2\text{H}$
	103	"	"	$\text{CH}_2\text{CONMe}_2$

	104 -CH ₂ -	"	
5	105 "	"	
	106 "		
10	107 -CH ₂ CH ₂ CH ₂ -		"
15	108 -CH ₂ CH- CH ₂ OH		"
20	109 -CH ₂ -		"
25			"
30			"

2360P/0840A

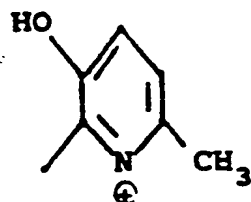
2361P/0840A

-76-

16622IH

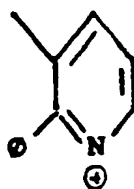
110 -CH₂-

5

CH₃

111 "

10



"

112 -CH₂CH₂CH₂-

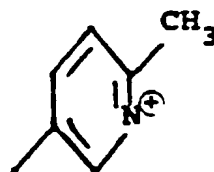
15



"

113 -CH₂CH₂-

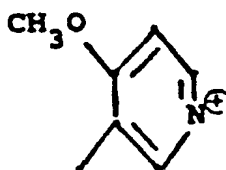
20



"

114 -CH₂-

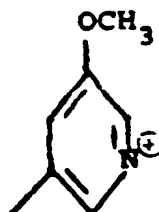
25



"

115 "

30



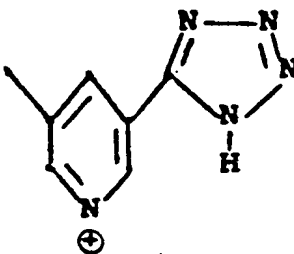
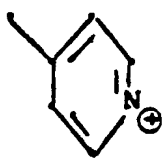
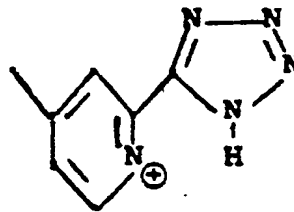
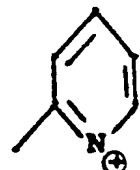
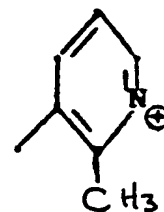

"

2360P/0840A

2361P/0840A

-77-

16622IH

5	116	$-\text{CH}_2-$		CH_3
10	117	$-\text{CH}_2\text{CH}_2\text{CH}_2-$		"
15	118	CH_2		"
20	119	bond		"
25	120	"		"
30	121	"		CH_3

2360P/0840A
2361P/0840A

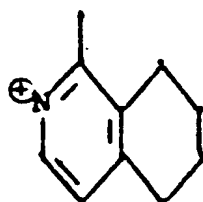
-78-

16622IH

122 bond

CH₃

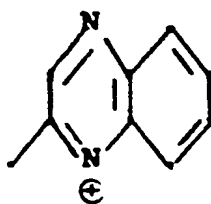
5

123 -CH₂-

"

10

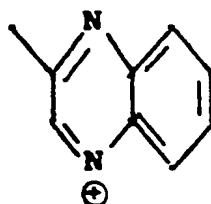
124 "



"

15

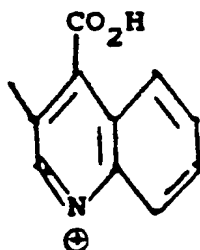
125 "



"

20

25 126 "



"

30

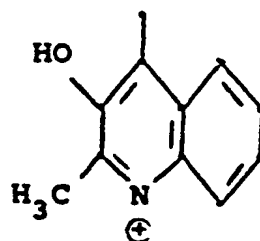
2360P/0840A
2361P/0840A

-79-

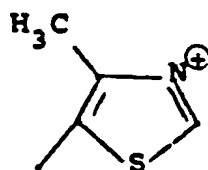
16622IH

127 -CH₂-

5

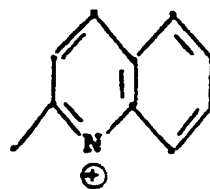
CH₃128 -CH₂CH₂-

10

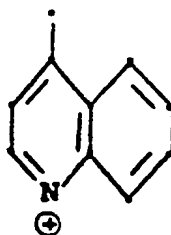


129 bond

15



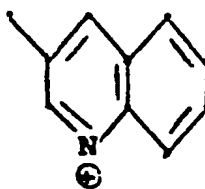
20 130 "



25

131 "

30



2360P/0840A
2361P/0840A

-80-

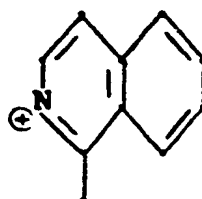
16622IH

132 bond

CH₃

5

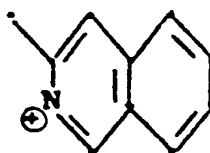
133 "



"

10

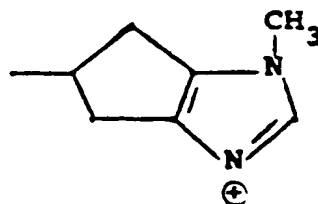
134 "



"

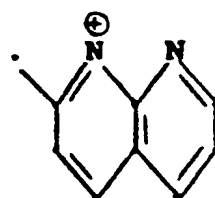
15

135 "



"

20

136 -CH-
CH₃

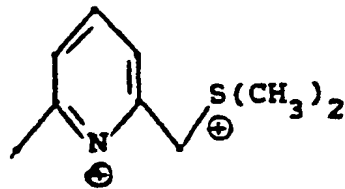
"

30

2360P/0840A
2361P/0840A

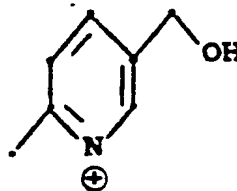
-81-

16622IH

137 -CH₂-CH₃

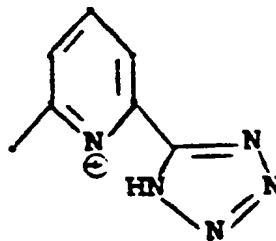
5

138 "



10

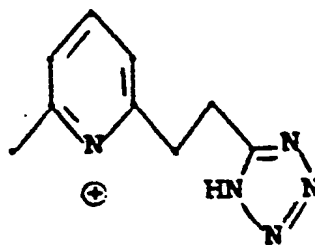
139 "



15

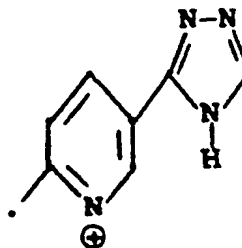
20

140 "



25

141 "



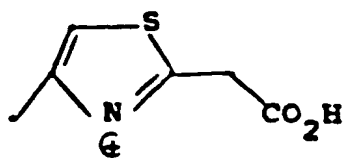
30

2360P/0840A

2361P/0840A

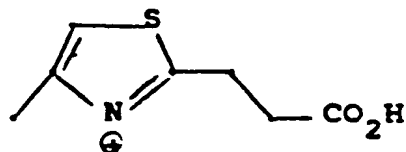
-82-

16622IH

142 CH₂CH₃

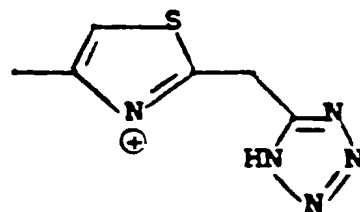
5

143 "



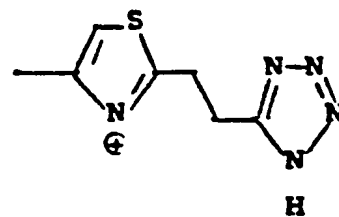
10

144 "



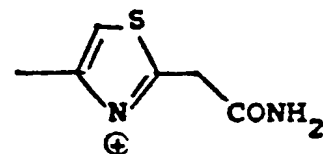
15

145 "



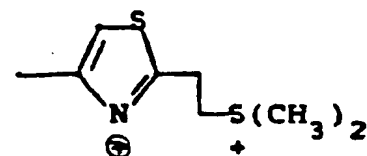
20

146 "



25

147 "



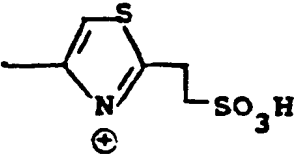
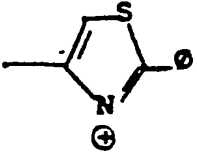
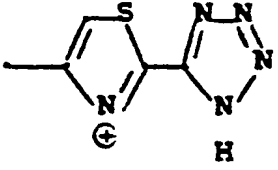
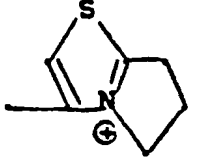
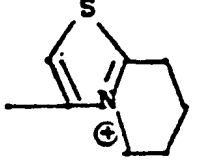
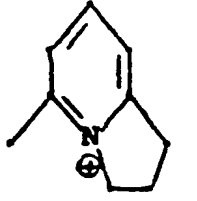
30

2360P/0840A

2361P/0840A

-83-

16622IH

148	-CH ₂ -		CH ₃
5			
149	"		"
10			
150	"		"
15			
151	"		--
20			
152	"		--
25			
153	"		--
30			

2360P/0840A

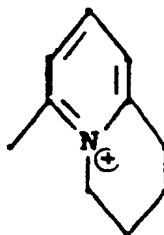
2361P/0840A

-84-

16622IH

154 -CH₂-

5



--

155 "

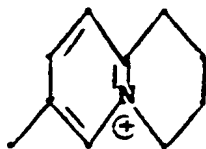
10



-

156 "

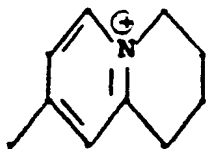
15



--

157 "

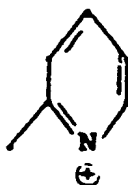
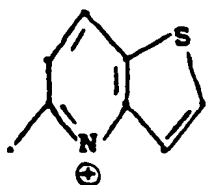
20



--

158 $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CHCH}_2- \end{array}$

25

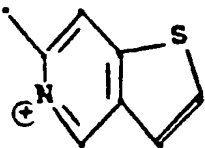
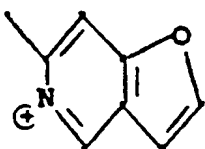
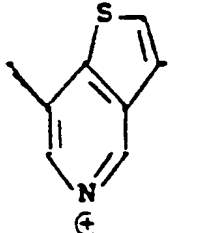
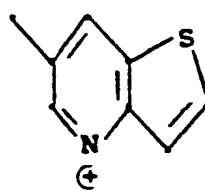
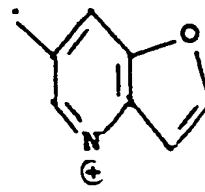
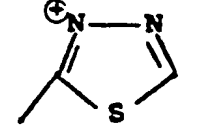
CH₃30 159 -CH₂-

"

2360P/0840A
2361P/0840A

-85-

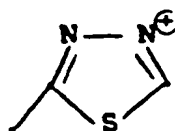
16622IH

	160	-CH ₂ -		CH ₃
5				
	161	"		"
10				
	162	"		"
15				
	163	"		"
20				
	164	"		"
25				
	165	"		"
30				

2360P/0840A
2361P/0840A

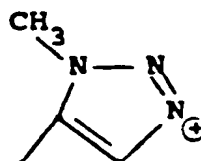
-86-

16622IH

166 -CH₂-CH₃

5

167 "



"

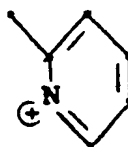
10

168 "

CH₂CONH₂

15

169 "



"

20

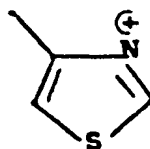
170 "



"

25

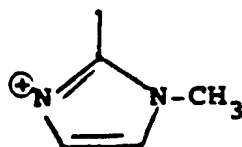
171 "



"

30

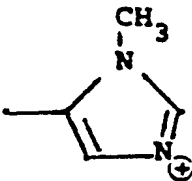
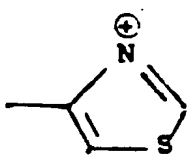

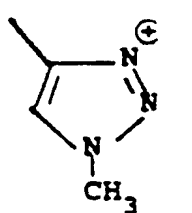
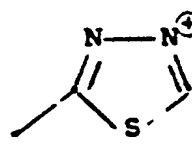
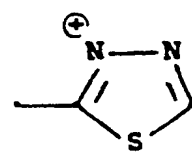
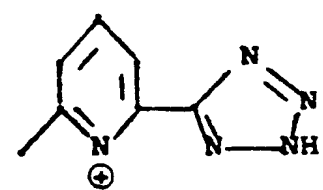
172 bond

CH₃

2360P/0840A
2361P/0840A

-87-

16622IH

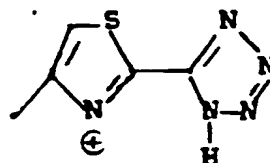
	173	bond		CH ₃
5				
	174	"		"
10				
	175	"		"
15				
	176	"		"
20				
	177	"		"
25				
	178	"		"
30				
	179	"		"

2360P/0840A

2361P/0840A

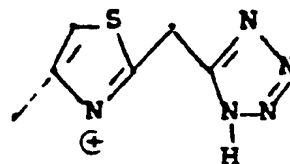
-88-

16622IH

180 -CH₂-CH₃

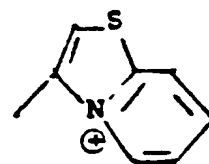
5

181 "



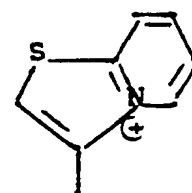
10

182 "

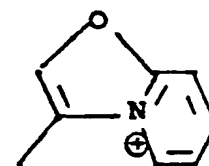


15

183 bond

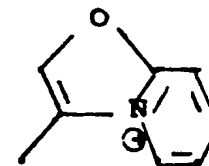


20

184 CH₂

25

185 bond



30

2360P/0840A

-89-

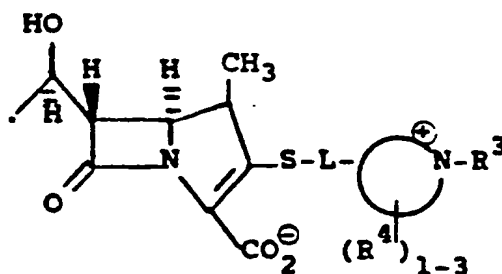
16622IH

2361P/0840A

EXAMPLE 12

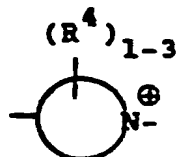
Utilizing the procedures of Examples 1- 10,
the following compounds are prepared:

5

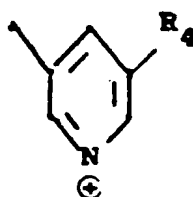


10

Com-
pound
No. L

R₃R₄

15

1 CH₂CH₃CO₂H

20

2 "

"

"

CONH₂

3 "

"

"

CN

25

4 "

"

"

OH

5 "

"

"

SO₂NH₂

30

6 "

"

"

SO₃H

7 "

"

"

NMe₂

8 "

"

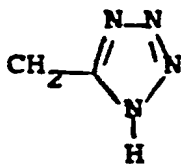
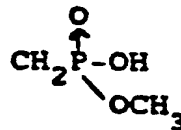
"

CONMe₂

2360P/0840A
2361P/0840A

-90-

16622IH

	9	"	"	"	CH_2NMe_2
	10	"	"	"	CH_2CN
5	11	"	"	"	CH_2CONH_2
	12	"	"	"	$\text{CH}_2\text{CO}_2\text{H}$
	13	"	"	"	CH_2SCH_3
10	14	"	"	"	CH_2SOCH_3
	15	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
15	16	"	"	"	SO_2CH_3
	17	"	"	"	SOCH_3
20	18	"	"	"	
	19	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
25	20	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	21	"	"	"	CH_2OCH_3
30	22	"	"	"	

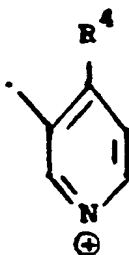
2360P/0840A

2361P/0840A

-91-

16622IH

	23	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	24	"	"	"	CF_3
5	25	"	"	"	CH_2OCNH_2
	26	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
10	27	"	"	"	Br
	28	"	"	"	Cl
	29	"	"	"	F
15	30	"	"	"	CO_2H
20					
	31	"	"	"	CONH_2
25	32	"	"	"	CN
	33	"	"	"	OH
30	34	"	"	"	SONH_2

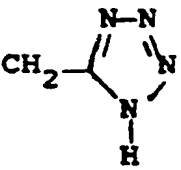


2360P/0840A

2361P/0840A

-92-

16622IH

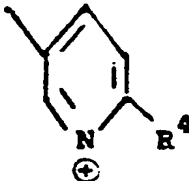
	35	"	"	"	SO ₃ H
	36	"	"	"	NMe ₂
5	37	"	"	"	CONMe ₂
	38	"	"	"	CH ₂ NMe ₂
	39	"	"	"	CH ₂ CN
10	40	"	"	"	CH ₂ CONH ₂
	41	"	"	"	CH ₂ CO ₂ H
15	41	"	"	"	CH ₂ SCH ₃
	43	"	"	"	CH ₂ SOCH ₃
	44	"	"	"	CH ₂ SO ₂ CH ₃
20	45	"	"	"	SO ₂ CH ₃
	46	"	"	"	SOCH ₃
25	47	"	"	"	 <chem>Cc1nn[nH]1</chem>
30	48	"	"	"	CH ₂ CH ₂ CO ₂ H
	49	"	"	"	CH ₂ SO ₃ H
	50	"	"	"	CH ₂ OCH ₃

2360P/0840A

2361P/0840A

-93-

16622IH

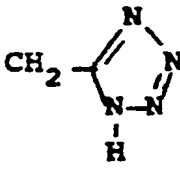
	51	"	"	"	$\text{CH}_2\overset{\text{O}}{\underset{\text{OCH}_3}{\text{P}}}\text{-OH}$
5	52	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	53	"	"	"	CF_3
10	54	"	"	"	$\text{CH}_2\overset{\text{O}}{\parallel}\text{OCNH}_2$
	55	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
15	56	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
	57	"		"	CO_2H
20	58	"	"	"	CONH_2
	59	"	"	"	CN
25	60	"	"	"	OCH_3
	61	"	"	"	SO_2NH_2
30	62	"	"	"	SO_3H
	63	"	"	"	NMe_2

2360P/0840A

2361P/0840A

-94-

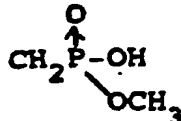
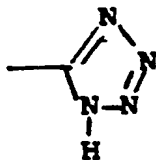

16622IH

	64	"	"	"	CONMe ₂
	65	"	"	"	CH ₂ NMe ₂
5	66	"	"	"	CH ₂ CN
	67	"	"	"	CH ₂ CONH ₂
	68	"	"	"	CH ₂ CO ₂ H
10	69	"	"	"	CH ₂ SCH ₃
	70	"	"	"	CH ₂ SOCH ₃
15	71	"	"	"	CH ₂ SO ₂ CH ₃
	72	"	"	"	SO ₂ CH ₃
	73	"	"	"	SOCH ₃
20	74	"	"	"	
25	75	"	"	"	CH ₂ CH ₂ CO ₂ H
	76	"	"	"	CH ₂ SO ₃ H
30	77	"	"	"	CH ₂ OCH ₃

2360P/0840A
2361P/0840A

-95-

16622IH

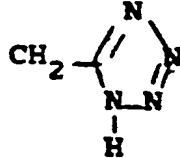
	78	"	"	"	
5	79	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	80	"	"	"	CF_3
10	81	"	"	"	$\text{CH}_2\text{OC(=O)NH}_2$
	82	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
	83	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
15					
	84	"	"	"	
20					
	85	"			"
25					
	86	"	"	"	CONH_2
	87	"	"	"	CN
30					
	88	"	"	"	OCH_3

2360P/0840A

2361P/0840A

-96-

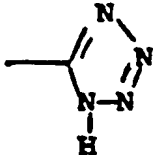
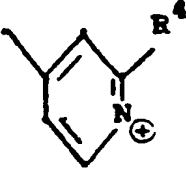
16622IH

	89	"	"	"	SO_2NH_2
	90	"	"	"	SO_3H
5	91	"	"	"	NMe_2
	92	"	"	"	CONMe_2
	93	"	"	"	CH_2NMe_2
10	94	"	"	"	CH_2CN
	95	"	"	"	CH_2CONH_2
15	96	"	"	"	$\text{CH}_2\text{CO}_2\text{H}$
	97	"	"	"	CH_2SCH_3
	98	"	"	"	CH_2SOCH_3
20	99	CH_3	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	100	"	"	"	SO_2CH_3
25	101	"	"	"	SOCH_3
	102	"	"	"	
30	103	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$

2360P/0840A
2361P/0840A

-97-

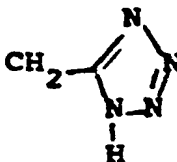
16622IH

	104	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	105	"	"	"	CH_2OCH_3
5	106	"	"	"	$\text{CH}_2\overset{\text{O}}{\underset{\text{OCH}_3}{\text{P}}}-\text{OH}$
	107	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
10	108	"	"	"	CF_3
	109	"	"	"	$\text{CH}_2\overset{\text{O}}{\text{C}}\text{NH}_2$
15	110	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
	111	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
20	112	"	"	"	
25	113	$-\text{CH}_2-$		"	CO_2H
30	114	"	"	"	CONH_2
	115	"	"	"	CN

2360P/0840A
2361P/0840A

-98-

16622IH

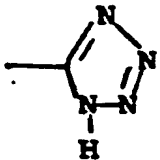
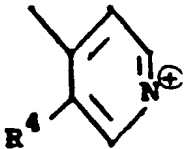
	116	"	"	"	OCH ₃
	117	"	"	"	SO ₂ NH ₂
5	118	"	"	"	SO ₃ H
	119	"	"	"	NMe ₂
	120	"	"	"	CONMe ₂
10	121	"	"	"	CH ₂ NMe ₂
	122	"	"	"	CH ₂ CN
15	123	"	"	"	CH ₂ CONH ₂
	124	"	"	"	CH ₂ CO ₂ H
	125	"	"	"	CH ₂ SCH ₃
20	126	"	"	"	CH ₂ SOCH ₃
	127	"	"	"	CH ₂ SO ₂ CH ₃
25	128	"	"	"	SO ₂ CH ₃
	129	"	"	"	SOCH ₃
30	130	"	"	"	

2360P/0840A

2361P/0840A

-99-

16622IH

	131	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
	132	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
5	133	"	"	"	CH_2OCH_3
	134	"	"	"	$\text{CH}_2\overset{\text{O}}{\underset{\text{OCH}_3}{\text{P}}}\text{-OH}$
10	135	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	136	"	"	"	CF_3
15	137	"	"	"	$\text{CH}_2\overset{\text{O}}{\parallel}\text{CONH}_2$
	138	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
20	139	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
	140	"	"	"	
25					
	141	"		"	CO_2H
30					
	142	"	"	"	CONH_2

2360P/0840A
2361P/0840A

-100-

16622IH

	143	"	"	"	CN
	144	"	"	"	OH
5	145	"	"	"	OCH ₃
	146	"	"	"	SO ₂ NH ₂
	147	"	"	"	SO ₃ H
10	148	"	"	"	NMe ₂
	149	"	"	"	CONMe ₂
15	150	"	"	"	CH ₂ NMe ₂
	151	"	"	"	CH ₂ CN
	152	"	"	"	CH ₂ CONH ₂
20	153	"	"	"	CH ₂ CO ₂ H
	154	"	"	"	CH ₂ SCH ₃
25	155	"	"	"	CH ₂ SOCH ₃
	156	"	"	"	CH ₂ SO ₂ CH ₃
	157	"	"	"	SO ₂ CH ₃
30	158	"	"	"	SOCH ₃

2360P/0840A

2361P/0840A

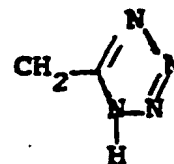
-101-

16622IH

159 "

"

"



5

160 "

"

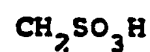
"



161 "

"

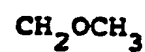
"



10 162 "

"

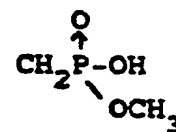
"



163 "

"

"

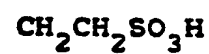


15

164 "

"

"



165 "

"

"



20

166 "

"

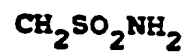
"



167 "

"

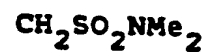
"



25 168 "

"

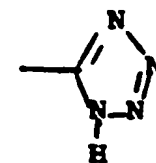
"



169 "

"

"



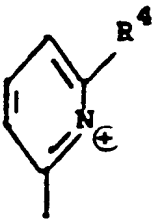
30

236CP/0840A

2361P/0840A

-102-

16622IH

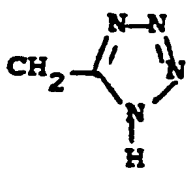
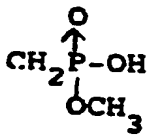

	170	"	"	"	F
	171	"	"	"	Cl
5	172	"	"	"	Br
10	173	"		"	CO ₂ H
	174	"	"	"	CONH ₂
15	175	"	"	"	CN
	176	"	"	"	SO ₂ NH ₂
20	177	"	"	"	SO ₃ H
	178	"	"	"	NMe ₂
	179	"	"	"	CONMe ₂
25	180	"	"	"	CH ₂ NMe ₂
	181	"	"	"	CH ₂ CN
30	182	"	"	"	CH ₂ CONH ₂
	183	"	"	"	CH ₂ CO ₂ H

2360P/0840A

2361P/0840A

-103-

16622IH

	184	"	"	"	CH_2SCH_3
	185	"	"	"	CH_2SOCH_3
5	186	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	187	"	"	"	SO_2CH_3
10	188	"	"	"	
	189	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
15	190	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	191	"	"	"	CH_2OCH_3
20	192	"	"	"	
	193	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
25	194	"	"	"	CF_3
	195	"	"	"	
30	196	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$

2360P/0840A

2361P/0840A

-104-

16622IH

5

197 "

" CO₂H

198 "

" CONH₂

10 199 "

" CN

200 "

" OH

201 "

" SO₂NH₂

15

202 "

" SO₃H

203 "

" NMe₂

20 204 "

" CONMe₂

205 "

" CH₂NMe₂

206 "

" CH₂CN

25

207 "

" CH₂CONH₂

208 "

" CH₂CO₂H

30 209 "

" CH₂SCH₃

210 "

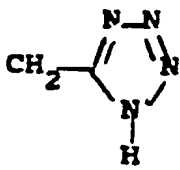
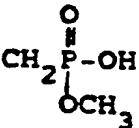

" CH₂SOCH₃

2360P/0840A

2361P/0840A

-105-

16622IH

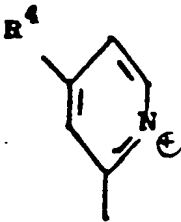
	211	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	212	"	"	"	SO_2CH_3
5	213	"	"	"	SOCH_3
10	214	"	"	"	
	215	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
15	216	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	217	"	"	"	CH_2OCH_3
20	218	"	"	"	
	219	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
25	220	"	"	"	CF_3
	221	"	"	"	
30	222	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
	223	"	"	"	Rr

2360P/0840A

2361P/0840A

-106-

16622IH

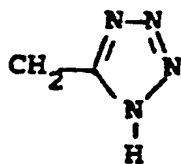
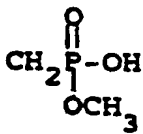
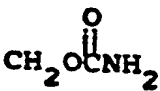
	224	"	"	"	Cl
	225	"	"	"	F
5	226	"		"	CO ₂ H
10	227	"	"	"	CONH ₂
	228	"	"	"	CN
15	229	"	"	"	SO ₂ NH ₂
	230	"	"	"	SO ₃ H
20	231	"	"	"	NMe ₂
	232	"	"	"	CONMe ₂
	233	"	"	"	CH ₂ NMe ₂
25	234	"	"	"	CH ₂ CN
	235	"	"	"	CH ₂ CONH ₂
30	236	"	"	"	CH ₂ CO ₂ H
	237	"	"	"	CH ₂ SCH ₃

2360P/0840A

2361P/0840A

-107-

16622IH

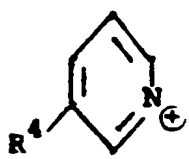
	238	"	"	"	CH_2SOCH_3
	239	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
5	240	"	"	"	SO_2CH_3
	241	"	"	"	SOCH_3
10	242	"	"	"	
	243	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
15	244	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	245	"	"	"	CH_2OCH_3
20	246	"	"	"	
	247	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
25	248	"	"	"	CF_3
	249	"	"	"	
30	250	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$

2360P/0840A

2361P/0840A

-108-

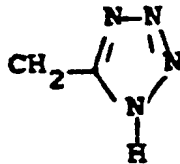
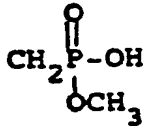
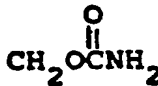
16622IH

5	251	"		"	CO ₂ H
	252	"	"	"	CONH ₂
10	253	"	"	"	CN
	254	"	"	"	OH
	255	"	"	"	SO ₂ NH ₂
15	256	"	"	"	SO ₃ H
	257	"	"	"	NMe ₂
20	258	"	"	"	CONMe ₂
	259	"	"	"	CH ₂ NMe ₂
	260	"	"	"	CH ₂ CN
25	261	"	"	"	CH ₂ CONH ₂
	262	"	"	"	CH ₂ CO ₂ H
30	263	"	"	"	CH ₂ SCH ₃
	264	"	"	"	CH ₂ SOCH ₃

2360P/0840A
2361P/0840A

-109-

16622IH

	265	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	266	"	"	"	SO_2CH_3
5	267	"	"	"	SOCH_3
10	268	"	"	"	
	269	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
	270	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
15	271	"	"	"	CH_2OCH_3
20	272	"	"	"	
	273	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
25	274	"	"	"	CF_3
	275	"	"	"	
30	276	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$

2360P/0840A

2361P/0840A

-110-

16622IH

277 "

"

"

Br

278 "

"

"

Cl

5 279 "

"

"

F

10

15

20

25

30

2360P/0840A

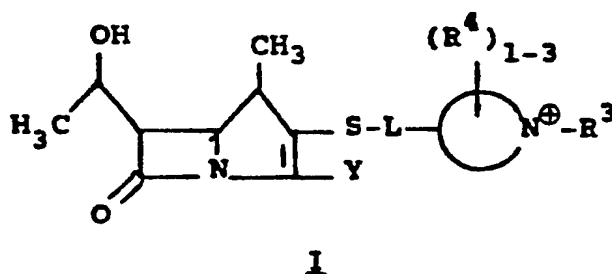
2361P/0840A

-111-

16622IH

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein:

L is a covalent bond or a bridging group selected from $-(CH_2)_{1-4}S-$; $-(CH_2)_{1-4}O-$; $-(CH_2)_{1-4}X-(CH_2)_{1-4}$ where X is O, S, NH, or $N(C_1-C_6)alkyl$; substituted or unsubstituted C_1-C_4 straight, C_1-C_6 branched or C_3-C_7 cycloalkyl groups wherein the substituents are selected from C_1-C_6 alkyl, $O-C_1-C_6$ alkyl, $S-C_1-C_6$ alkyl, halo, OH, CF_3 , CN, NH_2 , NHC_1-C_6 alkyl, $N(C_1-C_6 alkyl)_2$, CO_2H , $CONH_2$, $CONH(C_1-C_6 alkyl)$, and $CON(C_1-C_6 alkyl)_2$;

25

$(R^4)_{1-3}$ is a mono- or bicyclic heteroaryl group

containing from 5-11 ring atoms of which up to 5 are heteroatoms wherein R^3 is:

- 30
- 1) an unsubstituted or substituted C_1-C_6 alkyl radical;
 - 2) an unsubstituted or substituted C_1-C_6 alkenyl radical;

- 3) an unsubstituted or substituted C_1-C_6 alkynyl radical;
- 4) a C_3-C_7 cycloalkyl radical in which the ring is substituted or unsubstituted and one or more atoms may be replaced by a heteroatom;
- 5) a C_3-C_7 cycloalkyl methyl radical in which the ring may be substituted and one or more atoms may be replaced by a heteroatom;
- 6) an unsubstituted or substituted C_5-C_7 cycloalkenyl radical;
- 7) an unsubstituted or substituted bivalent C_2-C_6 alkylidene radical, optionally interrupted by a heteroatom, and joined to the heteroaryl group to form a ring which is carbocyclic or in which one or more atoms is replaced by a heteroatom. The new ring may contain one or more double bonds;
- 8) an unsubstituted or substituted phenyl or heteroaryl radical;
- 9) an unsubstituted or substituted phenyl (C_1-C_4 alkyl) or heteroaryl (C_1-C_4 alkyl) radical;
- 10) a cyano (C_1-C_4 alkyl) radical;
- 11) a carbamoyl (C_1-C_4 alkyl) radical;
- 12) a hydroxy (C_1-C_4 alkyl) radical;

-113-

13) an amino (C_1-C_4 alkyl) radical in which the nitrogen atom is unsubstituted or substituted with one to three C_1-C_4 alkyl groups;

14) an acidic side-chain of the structure

$-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

$n = 0-4$

$m = 0-4$

$X = CHR^3$, $CH=CH$, phenylene ($-C_6H_4-$), NH , $N(C_1-C_4 \text{ alkyl})$, O , S , $S-O$, $C=O$, SO_2 , SO_2NH , CO_2 , $CONH$, OCO , $OC=O$, $NHC=O$;

$R^3 = H$, $O(C_1-C_4 \text{ alkyl})$, NH , $NH(C_1-C_4 \text{ alkyl})$, $N(C_1-C_4 \text{ alkyl})$, CN , $CONH$, $CON(C_1-C_4 \text{ alkyl})$, CO_2H , SO_2NH , $SO_2NH(C_1-C_4 \text{ alkyl})$;

$Y = \text{single bond}$, NH , $N(C_1-C_4 \text{ alkyl})$, O , S ;

$A = \text{an acidic function such as carboxy } (CO_2H)$, phosphono $[P=O(OH)_2]$, alkylphosphono $\{P=O(OH)-[C(C_1-C_4 \text{ alkyl})]\}$, alkylphosphinyl $[P=O(OH)-(C_1-C_4 \text{ alkyl})]$, substituted phosphoramido $[P=O(OH)NH(C_1-C_4 \text{ alkyl}) \text{ and } P=O(OH)NHR^X]$, sulfinio (SO_2H), sulfo (SO_3H), 5-tetrazolyl (CN_4H), arylsulfonamido (SO_2NHR^X) and acylsulfonamides represented by the structures $CONHSO_2(C_1-C_4 \text{ alkyl})$, $CONHSO_2N(C_1-C_4 \text{ alkyl})_2$, $SO_2NHCO(C_1-C_4 \text{ alkyl})$ and SO_2NHCOR^X ;

$R^X = \text{aryl or heteroaryl as defined above}$;

wherein the substituents in the above definitions of R^3 are independently selected from the group consisting of the definitions of R^4 set out below;

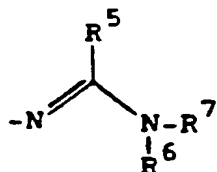
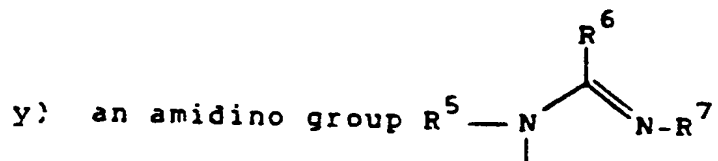
R^4 is independently selected from:

- a) a trifluoromethyl group;
- b) a halogen atom;
- c) an unsubstituted or substituted C_1-C_4 alkoxy radical;
- d) a hydroxy group;
- e) an unsubstituted or substituted (C_1-C_6 alkyl) carbonyloxy radical;
- f) a carbamoyloxy radical which is unsubstituted or substituted on nitrogen with one or two C_1-C_4 alkyl groups;
- g) a C_1-C_6 alkylthio radical, C_1-C_6 alkylsulfinyl radical or C_1-C_6 alkylsulfonyl radical, each of which is unsubstituted or substituted on the alkyl group;
- h) a sulfamoyl group which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;
- i) an amino group;

-115-

- j) a mono (C_1-C_4 alkyl) amino or di(C_1-C_4 alkyl)amino group, each of which is unsubstituted or substituted on the alkyl group;
- 5 k) a formylamino group;
- l) an unsubstituted or substituted (C_1-C_6 alkyl)carbonylamino radical;
- m) a (C_1-C_4 alkoxy) carbonylamino radical;
- 10 n) a ureido group in which the terminal nitrogen is unsubstituted or substituted with one or two C_1-C_4 alkyl groups;
- o) a (C_1-C_6 alkyl)sulfonamido group;
- 15 p) a cyano group;
- q) a formyl or acetalized formyl radical;
- r) an unsubstituted or substituted (C_1-C_6 alkyl)carbonyl radical
- 20 wherein the carbonyl is free or acetalized;
- s) an unsubstituted or substituted phenylcarbonyl or heteroarylcarbonyl radical;
- 25 t) a hydroximinomethyl radical in which the oxygen or carbon atom is optionally substituted by a C_1-C_4 alkyl group;
- u) a (C_1-C_6 alkoxy)carbonyl radical;
- 30 v) a carbamoyl radical which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;

- w) an N-hydroxycarbamoyl or N(C₁-C₄ alkoxy)carbamoyl radical in which the nitrogen atom may be additionally substituted by a C₁-C₄ alkyl group;
- x) a thiocarbamoyl group;



where R⁵, R⁶ and R⁷ are independently hydrogen, C₁-C₄ alkyl or wherein two of the alkyl groups together form a C₂-C₆ alkylidene radical optionally interrupted by a heteroatom and joined together to form a ring;

- z) a carboxamidino group
$$\begin{array}{c} \text{NR}^5 \\ || \\ \text{C} \\ / \quad \backslash \\ \text{NR}^6 \quad \text{R}^7 \end{array}$$
 where R⁵, R⁶ and R⁷ are as defined above;

- aa) a guanidinylyl group where R⁶ in ab) above is NR⁸R⁹ and R⁸ and R⁹ are as defined for R⁵ through R⁷ above.

- ab) hydrogen;
- ac) an unsubstituted or substituted
C₁-C₆ alkyl radical;
- ad) an unsubstituted or substituted
C₁-C₆ alkenyl radical;
- ae) an unsubstituted or substituted
C₁-C₆ alkynyl radical;
- af) a C₃-C₇ cycloalkyl radical in which
the ring is substituted or
unsubstituted and one or more atoms may
be replaced by a heteroatom;
- ag) a C₃-C₇ cycloalkyl methyl radical
in which the ring may be substituted
and one or more atoms may be replaced
by a heteroatom;
- ah) an unsubstituted or substituted
C₅-C₇ cycloalkenyl radical;
- ai) an unsubstituted or substituted phenyl
or heteroaryl radical;
- aj) an unsubstituted or substituted phenyl
(C₁-C₄ alkyl) or heteroaryl
(C₁-C₄ alkyl) radical; and

-118-

ak) an acidic side-chain of the structure

$-A$ or $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

$n = 0-4$

$m = 0-4$

$X = CHR^S, CH=CH, \text{phenylene } (-C_6H_4-), NH, N(C1-C4 \text{ alkyl}),$
 $O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;$
 $R^S = H, O(C1-C4 \text{ alkyl}), NH_2, NH(C1-C4 \text{ alkyl}), N(C1-C4 \text{ alkyl})_2,$
 $CN, CONH_2, CON(C1-C4 \text{ alkyl})_2, CO_2H, SO_2NH_2,$
 $SO_2NH(C1-C4 \text{ alkyl});$

$Y = \text{single bond}, NH, N(C1-C4 \text{ alkyl}), O, S;$

$A = \text{an acidic function such as carboxy } (CO_2H),$
 phosphono $[P=O(OH)_2],$ alkylphosphono $\{P=O(OH)-$
 $[C(C_1-C_4 \text{ alkyl})]\},$ alkylphosphinyl $[P=O(OH)-$
 $(C_1-C_4 \text{ alkyl})],$ substituted phosphoramido
 $[P=O(OH)NH(C_1-C_4 \text{ alkyl}) \text{ and } P=O(OH)NHP^X],$
 sulfinio $(SO_2H),$ sulfo $(SO_3H),$ 5-tetrazolyl
 $(CN_4H),$ arylsulfonamido (SO_2NHR^X) and acylsul-
 fonamides represented by the structures
 $CONHSO_2(C_1-C_4 \text{ alkyl}), CONHSO_2N(C_1-C_4 \text{ alkyl})_2 -$
 $SO_2NHCO(C_1-C_4 \text{ alkyl}) \text{ and } SO_2NHCOR^X;$
 $R^X = \text{aryl or heteroaryl as defined above};$

2360P/0840A

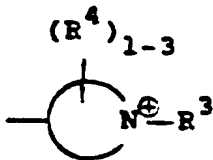
2361P/0840A

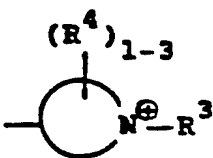
-119-

16622IH

- Y is selected from:
- i) COOH or a pharmaceutically acceptable ester or salt thereof,
 - ii) COOK¹ wherein R¹ is a removable carboxy protecting group,
 - iii) COOM wherein M is an alkali metal, or
 - iv) COO[⊖]; provided that when Y is other than iv) a counterion Z[⊖] is provided.

2. A compound of Claim 1 wherein L is substituted or unsubstituted branched or linear C₁-C₄ alkyl.

3. A compound of Claim 2 wherein  is monocyclic heteroarylium.

4. A compound of Claim 3 wherein  is a pyridinium group.

5. A compound of Claim 4 wherein R³ is an unsubstituted or substituted C₁-C₄ alkyl group.

2360P/0840A

2361P/0840A

-120-

16622IH

6. A compound of Claim 5 wherein L is

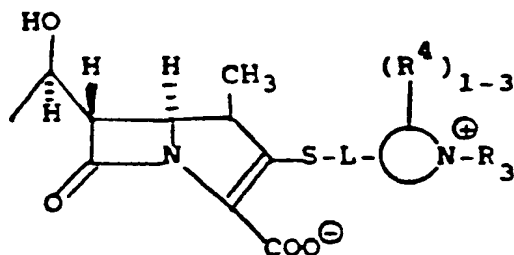
-CH₂-.

-CH(CH₃)- or -(CH₂)₂-.

5

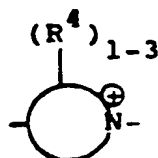
7. A compound of Claim 1 wherein the compound is a member selected from the group consisting of:

10



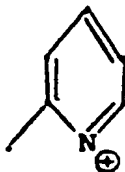
15

Com-
pound
No. L

R³

20

1 -CH₂-

CH₂CH₂CH₃

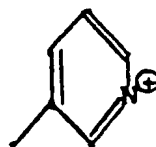
2 -CH -
|
CH₂CH₃

"

CH₂CH₃

25

3 -CH₂-

CH₂CH₂CH₃

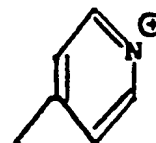
30

4 "

"

CH₂CH₃

5 "

CH₂CH₂CH₃

2360P/0840A

2361P/0840A

-121-

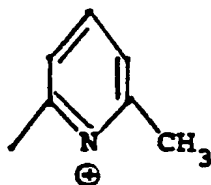
16622IH

6 -CH₂-

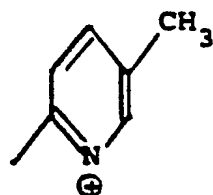
"

CH₂CH₃

5 7 "

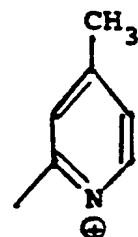
CH₃

10 8 "



"

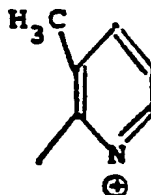
15 9 "



"

20

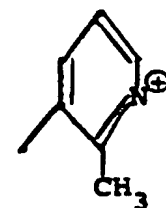
10 "



"

25

30 11 "



"

2360P/0840A

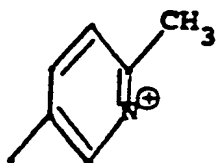
2361P/0840A

-122-

0170073

16622IH

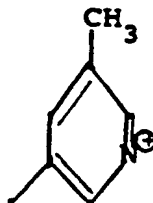
12 -CH₂-



CH₃

5

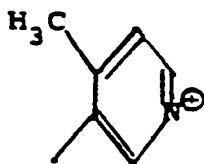
13 "



"

10

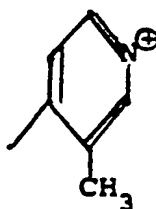
14 "



"

15

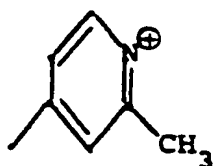
15 "



"

20

16 "



"

25

17 -CH₂CH₂-



CH₂CH₃

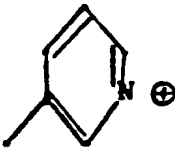
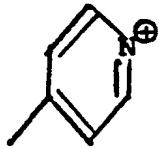
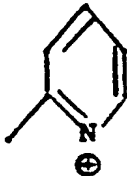
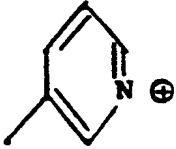

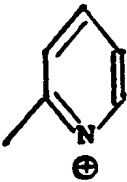
30

2360P/0840A

2361P/0840A

-123-

16622IH

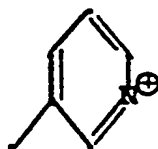
18	-CH ₂ CH ₂ -		CH ₃
5			
19	"		"
10			
20	-CH- CH ₃		"
15			
21	"		"
20			
22	"		"
25			
23	-CH ₂ -		ØCH ₂
30			

2360P/0840A

2361P/0840A

-124-

16622IH

24 -CH₂-ØCH₂.

5

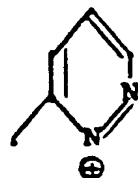
25 "



"

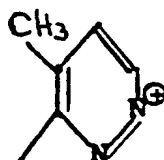
10

26 "

CH₃

15

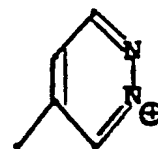
27 "



"

20

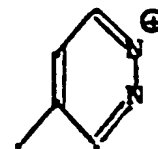
28 "



"

25

29 "



"


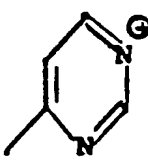
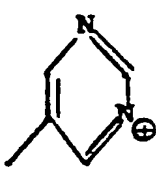
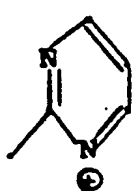
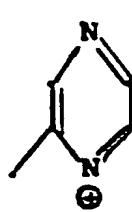
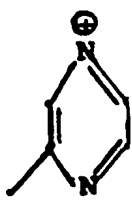
30

2360P/0840A

2361P/0840A

-125-

16622IH

5	30	-CH ₂ -		CH ₃
10	31	"		"
15	32	"		"
20	33	"		"
25	34	"		"
30	35	"		"

2360P/0840A

2361P/0840A

-126-

16622IH

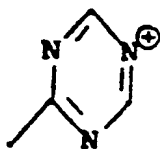
36 -CH₂-

5

CH₃

37 "

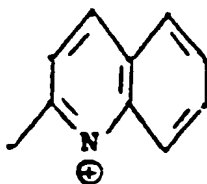
10



"

38 "

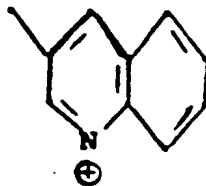
15



"

39 "

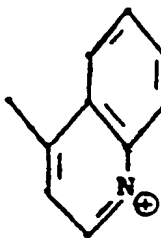
20



"

25 40 "

30



"

41 "



"

2360P/0840A

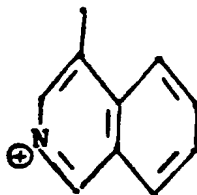
2361P/0840A

-127-

16622IH

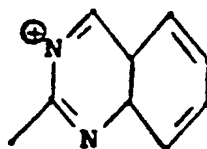
42 -CH₂-

5

CH₃

43 "

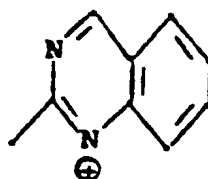
10



"

44 "

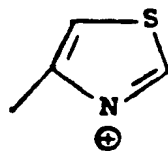
15



"

45 "

20

CH₂CH₂CH₃

46 "

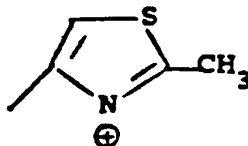
25

"

CH₂CH₃

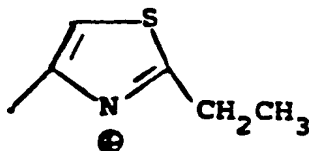
47 "

47

CH₃

30

48 "



"

2360P/0840A

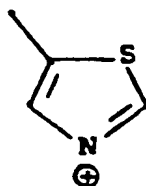
2361P/0840A

-128-

16622IH

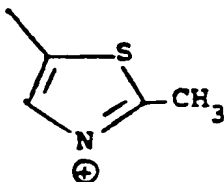
49 -CH₂-

5

CH₃

50 "

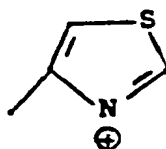
10



"

51 -CH-
CH₃

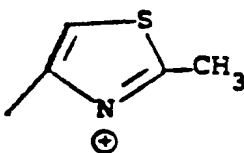
15



"

52 "

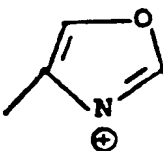
20



"

53 -CH₂-

25



"

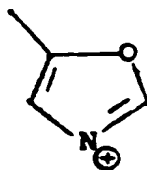
54 "

30

"

CH₂CH₃

55 "

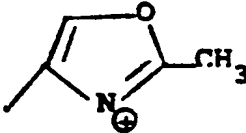
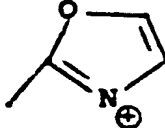
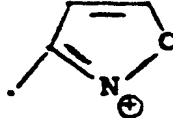
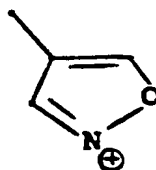
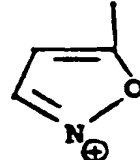
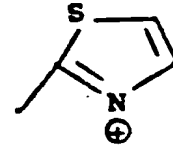
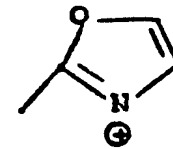
CH₃

2360P/0840A

2361P/0840A

-129-

16622IH

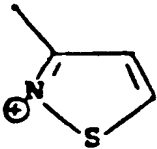
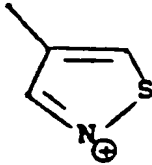
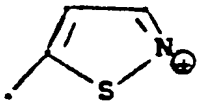
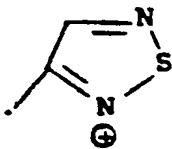
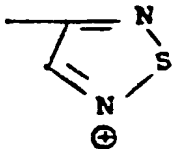
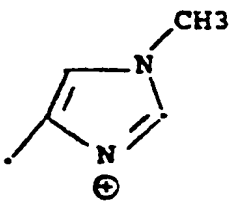
56	-CH ₂ -		CH ₃
57	"		"
58	"		"
59	"		"
60	"		"
61	"		CH ₂ CH ₃
62	-CH ₂ CH ₂ -		CH ₃

2360P/0840A

2361P/0840A

-130-

16622IH

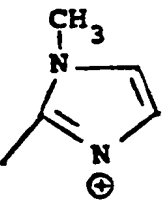
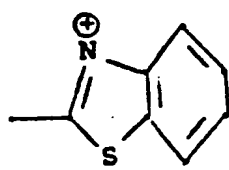
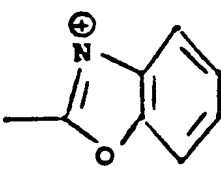
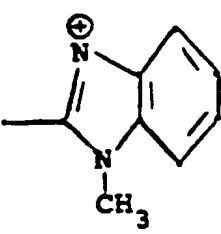

63	-CH ₂ -		CH ₃
5			
64	"		"
10			
65	"		"
15			
66	"		"
20			
67	"		"
25			
68	"		CH ₃
30			
69	"	"	-CH ₂ CH ₃

2360P/0840A

2361P/0840A

-131-

16622IH

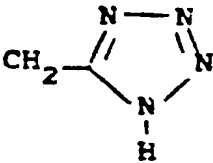
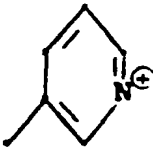
5	70	-CH ₂ -		-CH ₃ .
10	71	"		"
15	72	"		"
20	73	"		"
25	74	"		CH ₂ OCH ₃
	75	"	"	CH ₂ CN
30	76	"	"	CH ₂ CO ₂ H
	77	"	"	CH ₂ SO ₂ CH ₃

2360P/0840A
2361P/0840A

-132-

0170073

16622IH

5	78	-CH ₂ -	"	$\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{P}}}(\text{OH})\text{OCH}_3$
	79	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	80	"	"	$\text{CH}_2\text{CONMe}_2$
	81	"	"	CH_2SOCH_3
	10 82	"	"	CH_2NMe_2
15	83	"	"	
	20 84	"		CH_2OCH_3
25	85	"	"	CH_2SCH_3
	86	"	"	CH_2SOCH_3
	87	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	88	"	"	$\text{CH}_2\text{CO}_2\text{H}$
	30 89	"	"	$\text{CH}_2\text{CONMe}_2$

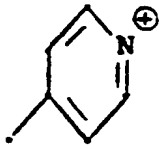
0170073

2360P/0840A

2361P/0840A

-133-

16622IH

	90	-CH ₂ -	"	$\text{CH}_2\overset{\text{O}}{\underset{\uparrow}{\text{P}}}(\text{OH})\text{OCH}_3$
5	91	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	92	"	"	CH_2CN
	93	"	"	CH_2NMe_2
10	94	"	"	$\text{CH}_2\text{CH}_2\text{NMe}_2$
15	95	"		CH_2OCH_3
	96	"	"	CH_2NMe_2
20	97	"	"	$\text{CH}_2\text{CH}_2\text{NMe}_2$
	98	"	"	CH_2CN
	99	"	"	CH_2SCH_3
25	100	"	"	CH_2SOCH_3
	101	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
30	102	"	"	$\text{CH}_2\text{CO}_2\text{H}$
	103	"	"	$\text{CH}_2\text{CONMe}_2$

2360P/0840A

2361P/0840A

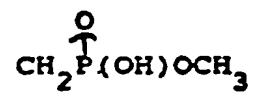
-134-

16622IH

5

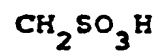
104 -CH₂-

"



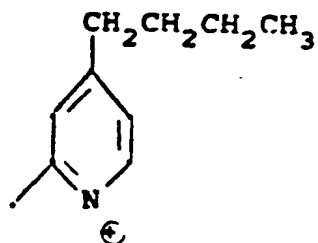
105 "

"

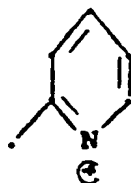


10

106 "

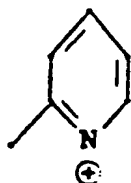


15

107 -CH₂CH₂CH₂-

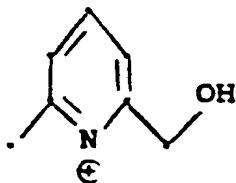
"

20

108 -CH₂CH-
CH₂OH

"

25

109 -CH₂-

"

30

2360P/0840A

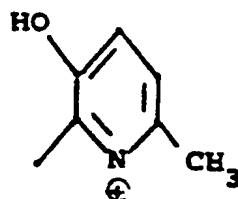
2361P/0840A

-135-

16622IH

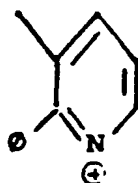
110 -CH₂-

5

CH₃

111 "

10



"

112 -CH₂CH₂CH₂-

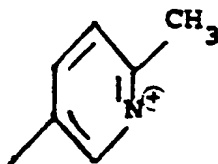
15



"

113 -CH₂CH₂-

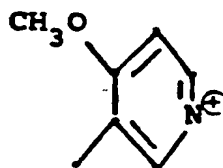
20



"

114 -CH₂-

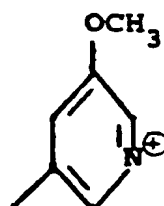
25



"

115 "

30



"

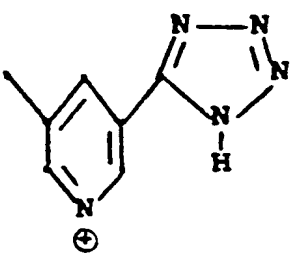
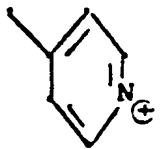
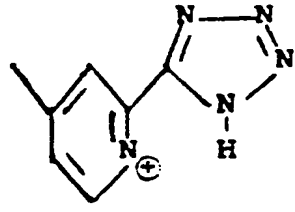
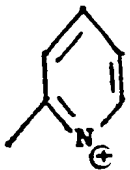
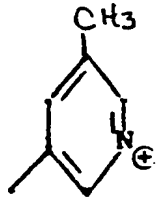

0170073

2360P/0840A

2361P/0840A

-136-

16622IH

5	116	-CH ₂ -		CH ₃
10	117	-CH ₂ CH ₂ CH ₂ -		"
15	118	CH ₂		"
20	119	bond		"
25	120	"		"
30	121	"		CH ₃

2360P/0840A
2361P/0840A

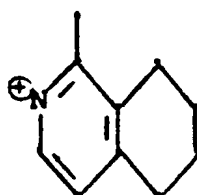
-137-

16622IH

122 bond

CH₃

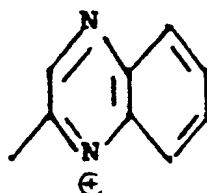
5

123 -CH₂-

"

10

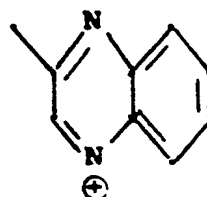
124 "



"

15

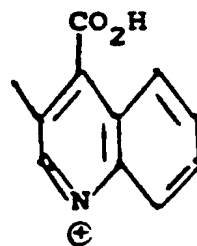
125 "



"

20

25 126 "



"

30

2360P/0840A

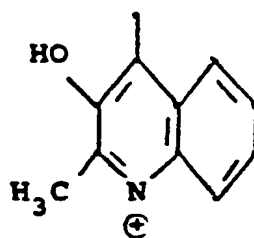
2361P/0840A

-138-

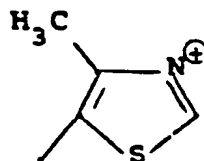
16622IH

127 -CH₂-

5

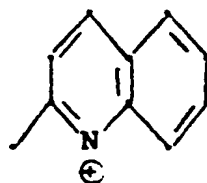
CH₃128 -CH₂CH₂-

10

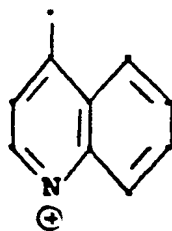


129 bond

15

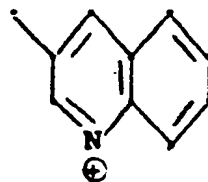


20 130 "



25

131 "



30

0170073

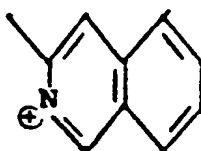
2360P/0840A

2361P/0840A

-139-

16622IH

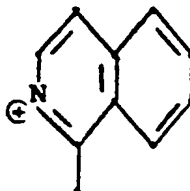
132 bond



CH₃

5

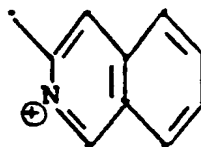
133 "



"

10

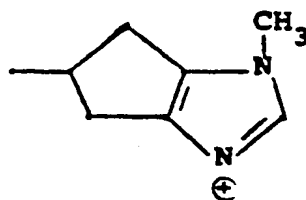
134 "



"

15

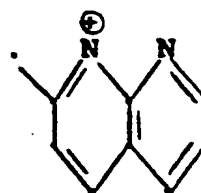
135 "



"

20

136 -CH-
CH₃



"

25

30

2360P/0840A

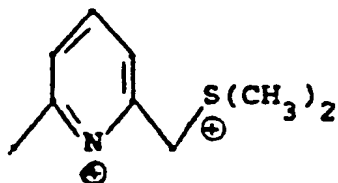
2361P/0840A

0170073

-140-

16622IH

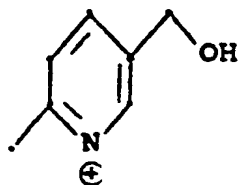
137 -CH₂-



CH₃

5

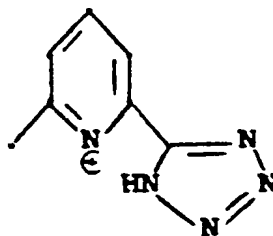
138 "



"

10

139 "

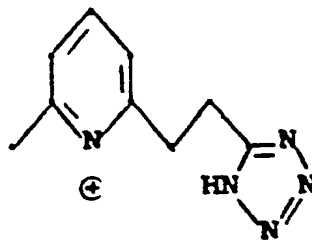


"

15

20

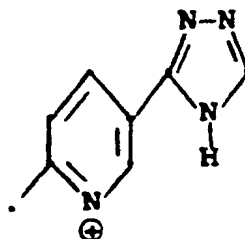
140 "



"

25

141 "



"

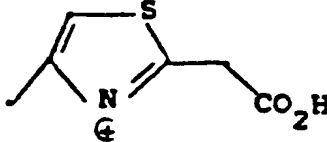
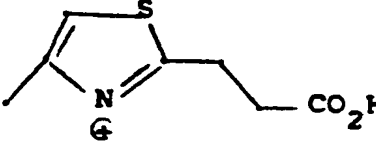
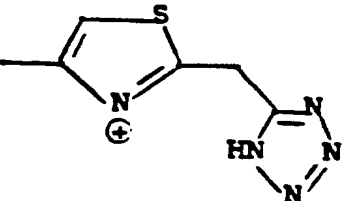
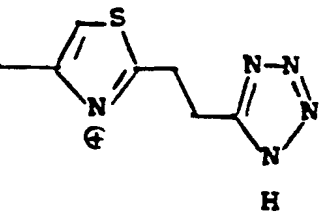
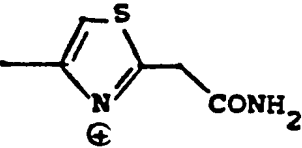
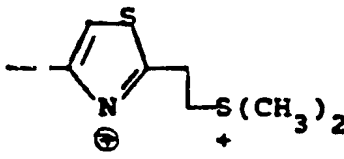
30

2360P/0840A

2361P/0840A

-141-

16622IH

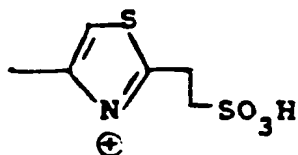
142	CH ₂		CH ₃
5			
143	"		"
10			
144	"		"
15			
145	"		"
20			
146	"		"
25			
147	"		"
30			

2360P/0840A

2361P/0840A

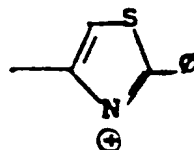
16622IH

-142-

148 -CH₂-CH₃

5

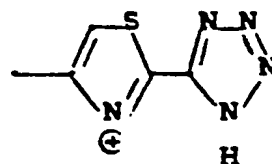
149 "



"

10

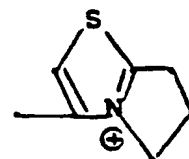
150 "



"

15

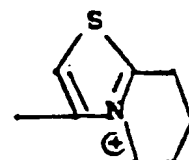
151 "



--

20

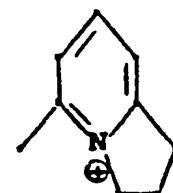
152 "



--

25

153 "



--

30

2360P/0840A

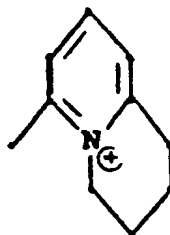
2361P/0840A

-143-

16622IH

154 -CH₂-

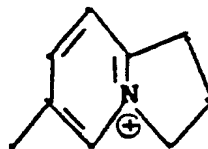
5



--

155 "

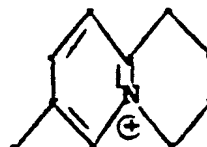
10



-

156 "

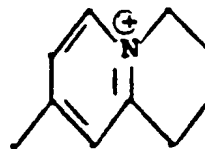
15



--

157 "

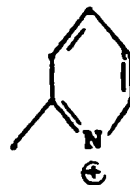
20



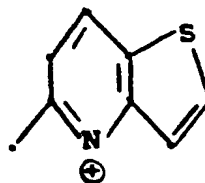
--

158 $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CHCH}_2- \end{array}$

25

CH₃159 -CH₂-

30



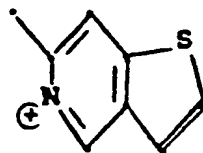
"

2360P/0840A

2361P/0840A

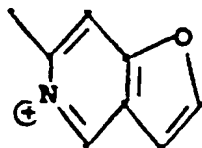
-144-

16622IH

160 -CH₂-CH₃

5

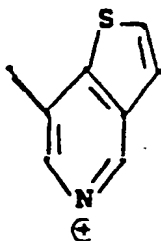
161 "



"

10

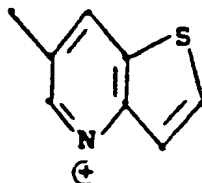
162 "



"

15

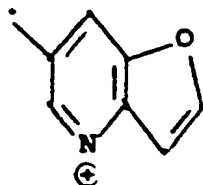
163 "



"

20

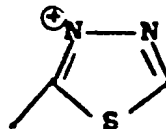
25 164 "



"

30

165 "



"


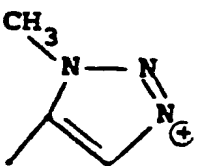
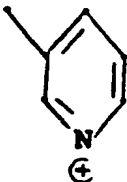
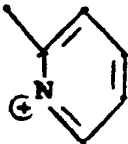

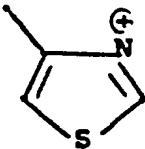
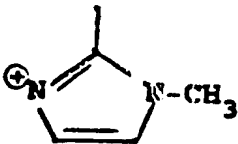
0170073

2360P/0840A

2361P/0840A

-145-

16622IH

	166	-CH ₂ -		CH ₃
5	167	"		"
10	168	"		CH ₂ CONH ₂
15	169	"		"
20	170	"		"
25	171	"		"
30	172	bond		CH ₃

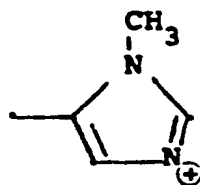
2360P/0840A

2361P/0840A

-146-

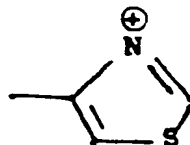
16622IH

173 bond

CH₃

5

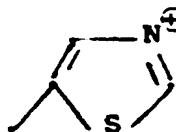
174 "



"

10

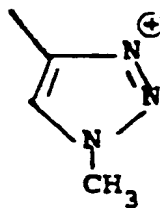
175 "



"

15

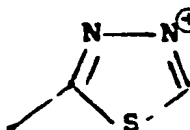
176 "



"

20

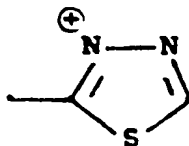
177 "



"

25

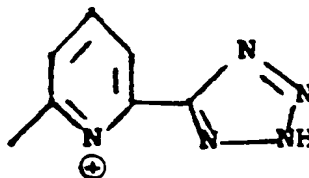
178 "



"

30

179 "



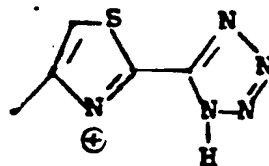
"

2360P/0840A

2361P/0840A

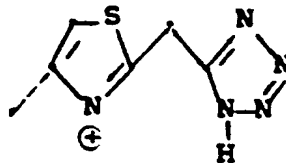
-147-

16622IH

180 -CH₂-CH₃

5

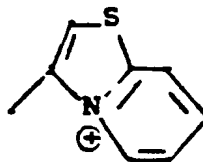
181 "



"

10

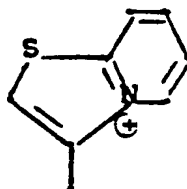
182 "



--

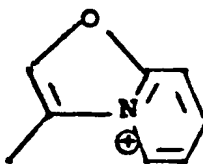
15

183 bond



--

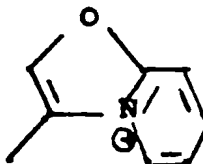
20

184 CH₂

--

25

185 bond



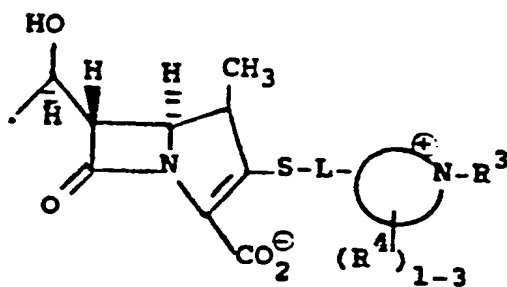
--

30

-148-

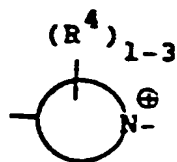
16622IH

5

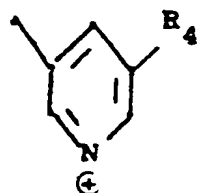


10

Com-
pound
No. L

 R_3 R_4

15

1 CH_2  CH_3 CO_2H

20

2 "

"

"

 $CONH_2$

3 "

"

"

CN

25

4 "

"

"

OH

5 "

"

"

 SO_2NH_2

30

6 "

"

"

 SO_3H

7 "

"

"

 NMe_2

8 "

"

"

 $CONMe_2$

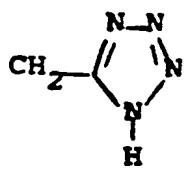
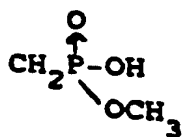
0170073

2360P/0840A

2361P/0840A

-149-

16622IH

	9	"	"	"	CH_2NMe_2
	10	"	"	"	CH_2CN
5	11	"	"	"	CH_2CONH_2
	12	"	"	"	$\text{CH}_2\text{CO}_2\text{H}$
10	13	"	"	"	CH_2SCH_3
	14	"	"	"	CH_2SOCH_3
	15	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
15	16	"	"	"	SO_2CH_3
	17	"	"	"	SOCH_3
20	18	"	"	"	
25	19	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
	20	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	21	"	"	"	CH_2OCH_3
30	22	"	"	"	

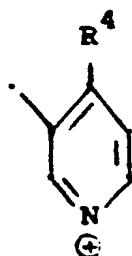
2360P/0840A

2361P/0840A

-150-

16622IH

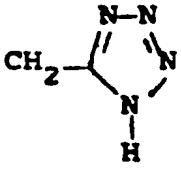
	23	"	"	"	CH ₂ CH ₂ SO ₃ H
	24	"	"	"	CF ₃
5	25	"	"	"	CH ₂ OC(=O)NH ₂
	26	"	"	"	CH ₂ SO ₂ NH ₂
10	27	"	"	"	Br
	28	"	"	"	Cl
	29	"	"	"	F
15	30	"	"	"	CO ₂ H
20	31	"	"	"	CONH ₂
25	32	"	"	"	CN
	33	"	"	"	OH
30	34	"	"	"	SONH ₂



2360P/0840A
2361P/0840A

-151-

16622IH

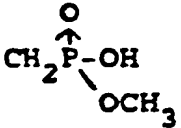
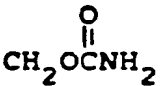
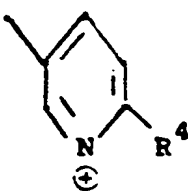
	35	"	"	"	SO ₃ H
	36	"	"	"	NMe ₂
5	37	"	"	"	CONMe ₂
	38	"	"	"	CH ₂ NMe ₂
	39	"	"	"	CH ₂ CN
10	40	"	"	"	CH ₂ CONH ₂
	41	"	"	"	CH ₂ CO ₂ H
15	41	"	"	"	CH ₂ SCH ₃
	43	"	"	"	CH ₂ SOCH ₃
	44	"	"	"	CH ₂ SO ₂ CH ₃
20	45	"	"	"	SO ₂ CH ₃
	46	"	"	"	SOCH ₃
25	47	"	"	"	
30	48	"	"	"	CH ₂ CH ₂ CO ₂ H
	49	"	"	"	CH ₂ SO ₃ H
	50	"	"	"	CH ₂ OCH ₃

2360P/0840A

2361P/0840A

-152-

16622IH

	51	"	"	"	
5	52	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	53	"	"	"	CF_3
10	54	"	"	"	
	55	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
	56	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
15					
	57	"		"	CO_2H
20					
	58	"	"	"	CONH_2
	59	"	"	"	CN
25					
	60	"	"	"	OCH_3
	61	"	"	"	SO_2NH_2
30	62	"	"	"	SO_3H
	63	"	"	"	NMe_2

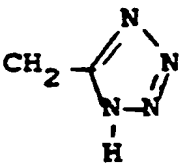
0170073

2360P/0840A

2361P/0840A

-153-

16622IH

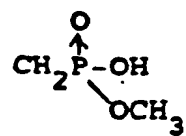
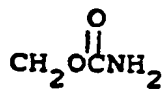
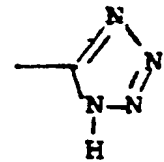
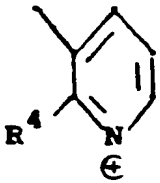
	64	"	"	"	CONMe ₂
	65	"	"	"	CH ₂ NMe ₂
5	66	"	"	"	CH ₂ CN
	67	"	"	"	CH ₂ CONH ₂
	68	"	"	"	CH ₂ CO ₂ H
10	69	"	"	"	CH ₂ SCH ₃
	70	"	"	"	CH ₂ SOCH ₃
15	71	"	"	"	CH ₂ SO ₂ CH ₃
	72	"	"	"	SO ₂ CH ₃
	73	"	"	"	SOCH ₃
20	74	"	"	"	
25	75	"	"	"	CH ₂ CH ₂ CO ₂ H
	76	"	"	"	CH ₂ SO ₃ H
30	77	"	"	"	CH ₂ OCH ₃

2360P/0840A

2361P/0840A

-154-

16622IH

	78	"	"	"	
5	79	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	80	"	"	"	CF_3
10	81	"	"	"	
	82	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
15	83	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
	84	"	"	"	
20					
	85	"		"	CO_2H
25					
	86	"	"	"	CONH_2
	87	"	"	"	CN
30					
	88	"	"	"	OCH_3

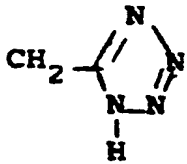
0170073

2360P/0840A

2361P/0840A

-155-

16622IH

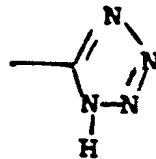
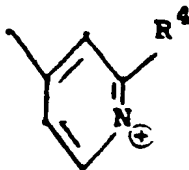
	89	"	"	"	SO_2NH_2
	90	"	"	"	SO_3H
5	91	"	"	"	NMe_2
	92	"	"	"	CONMe_2
	93	"	"	"	CH_2NMe_2
10	94	"	"	"	CH_2CN
	95	"	"	"	CH_2CONH_2
15	96	"	"	"	$\text{CH}_2\text{CO}_2\text{H}$
	97	"	"	"	CH_2SCH_3
	98	"	"	"	CH_2SOCH_3
20	99	CH_3	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	100	"	"	"	SO_2CH_3
25	101	"	"	"	SOCH_3
	102	"	"	"	
30	103	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$

2360P/0840A

2361P/0840A

-156-

16622IH

	104	"	"	"	CH ₂ SO ₃ H
	105	"	"	"	CH ₂ OCH ₃
5	106	"	"	"	$\begin{array}{c} \text{O} \\ \uparrow \\ \text{CH}_2\text{P}-\text{OH} \\ \quad \quad \quad \backslash \\ \quad \quad \quad \text{OCH}_3 \end{array}$
	107	"	"	"	CH ₂ CH ₂ SO ₃ H
10	108	"	"	"	CF ₃
	109	"	"	"	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{OCNH}_2 \end{array}$
15	110	"	"	"	CH ₂ SO ₂ NH ₂
	111	"	"	"	CH ₂ SO ₂ NMe ₂
20	112	"	"	"	
25	113	-CH ₂ -		"	CO ₂ H
30	114	"	"	"	CONH ₂
	115	"	"	"	CN

2360P/0840A

2361P/0840A

-157-

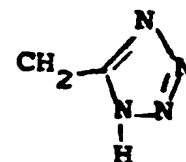
16622IH

	116	"	"	"	OCH ₃
	117	"	"	"	SO ₂ NH ₂
5	118	"	"	"	SO ₃ H
	119	"	"	"	NMe ₂
	120	"	"	"	CONMe ₂
10	121	"	"	"	CH ₂ NMe ₂
	122	"	"	"	CH ₂ CN
15	123	"	"	"	CH ₂ CONH ₂
	124	"	"	"	CH ₂ CO ₂ H
	125	"	"	"	CH ₂ SCH ₃
20	126	"	"	"	CH ₂ SOCH ₃
	127	"	"	"	CH ₂ SO ₂ CH ₃
25	128	"	"	"	SO ₂ CH ₃
	129	"	"	"	SOCH ₃

30 130 "

"

"



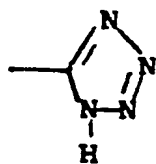
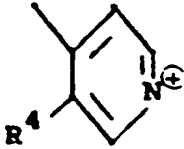
0170073

2360P/0840A

2361P/0840A

-158-

16622IH

	131	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
	132	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
5	133	"	"	"	CH_2OCH_3
	134	"	"	"	$\text{CH}_2\overset{\text{O}}{\underset{\text{OCH}_3}{\text{P}}}-\text{OH}$
10	135	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	136	"	"	"	CF_3
15	137	"	"	"	$\text{CH}_2\overset{\text{O}}{\parallel}\text{CNH}_2$
	138	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
20	139	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
25	140	"	"	"	
30	141	"		"	CO_2H
	142	"	"	"	CONH_2

2360P/0840A

2361P/0840A

-159-

16622IH

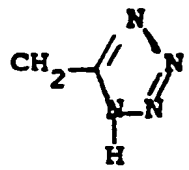
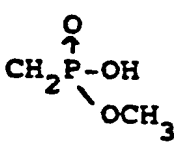
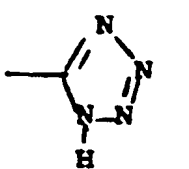
	143	"	"	"	CN
	144	"	"	"	OH
5	145	"	"	"	OCH ₃
	146	"	"	"	SO ₂ NH ₂
	147	"	"	"	SO ₃ H
10	148	"	"	"	NMe ₂
	149	"	"	"	CONMe ₂
15	150	"	"	"	CH ₂ NMe ₂
	151	"	"	"	CH ₂ CN
	152	"	"	"	CH ₂ CONH ₂
20	153	"	"	"	CH ₂ CO ₂ H
	154	"	"	"	CH ₂ SCH ₃
25	155	"	"	"	CH ₂ SOCH ₃
	156	"	"	"	CH ₂ SO ₂ CH ₃
	157	"	"	"	SO ₂ CH ₃
30	158	"	"	"	SOCH ₃

2360P/0840A

2361P/0840A

-160-

16622IH

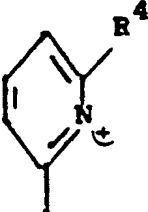
	159	"	"	"	
5	160	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
	161	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
10	162	"	"	"	CH_2OCH_3
	163	"	"	"	
15	164	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	165	"	"	"	CF_3
20	166	"	"	"	$\text{CH}_2\text{OC(=O)NH}_2$
	167	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
25	168	"	"	"	$\text{CH}_2\text{SO}_2\text{NMe}_2$
30	169	"	"	"	

2360P/0840A

2361P/0840A

-161-

16622IH

	170	"	"	"	F
	171	"	"	"	Cl
5	172	"	"	"	Br
10	173	"		"	CO ₂ H
	174	"	"	"	CONH ₂
15	175	"	"	"	CN
	176	"	"	"	SO ₂ NH ₂
20	177	"	"	"	SO ₃ H
	178	"	"	"	NMe ₂
	179	"	"	"	CONMe ₂
25	180	"	"	"	CH ₂ NMe ₂
	181	"	"	"	CH ₂ CN
30	182	"	"	"	CH ₂ CONH ₂
	183	"	"	"	CH ₂ CO ₂ H

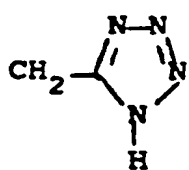
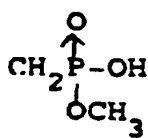
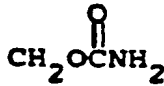
0170073

2360P/0840A

2361P/0840A

-162-

16622IH

	184	"	"	"	CH_2SCH_3
	185	"	"	"	CH_2SOCH_3
5	186	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	187	"	"	"	SO_2CH_3
10	188	"	"	"	
	189	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
15	190	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	191	"	"	"	CH_2OCH_3
20	192	"	"	"	
	193	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
25	194	"	"	"	CF_3
	195	"	"	"	
30	196	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$

2360P/0840A

2361P/0840A

-163-

16622IH

5

197

"



"

 CO_2H

10

198

"

"

"

 CONH_2

15

199

"

"

"

 CN

200

"

"

"

 OH

20

201

"

"

"

 SO_2NH_2

202

"

"

"

 SO_3H

203

"

"

"

 NMe_2

25

204

"

"

"

 CONMe_2

205

"

"

"

 CH_2NMe_2

206

"

"

"

 CH_2CN

30

207

"

"

"

 CH_2CONH_2

208

"

"

"

 $\text{CH}_2\text{CO}_2\text{H}$

209

"

"

"

 CH_2SCH_3

210

"

"

"

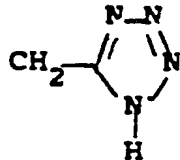
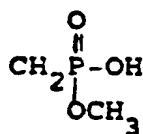
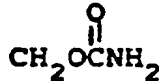
 CH_2SOCH_3

2360P/0840A

2361P/0840A

-164-

16622IH

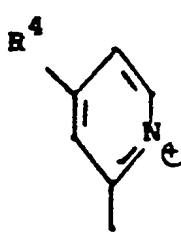
	211	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	212	"	"	"	SO_2CH_3
5	213	"	"	"	SOCH_3
10	214	"	"	"	
	215	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
15	216	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	217	"	"	"	CH_2OCH_3
20	218	"	"	"	
	219	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
25	220	"	"	"	CF_3
	221	"	"	"	
30	222	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
	223	"	"	"	Br

2360P/0840A

2361P/0840A

-165-

16622IH

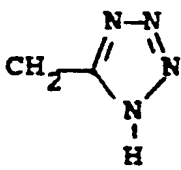
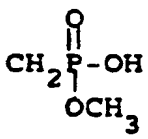
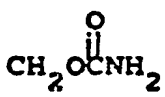
	224	"	"	"	Cl
	225	"	"	"	F
5	226	"		"	CO ₂ H
10	227	"	"	"	CONH ₂
	228	"	"	"	CN
15	229	"	"	"	SO ₂ NH ₂
	230	"	"	"	SO ₃ H
	231	"	"	"	NMe ₂
20	232	"	"	"	CONMe ₂
	233	"	"	"	CH ₂ NMe ₂
25	234	"	"	"	CH ₂ CN
	235	"	"	"	CH ₂ CONH ₂
	236	"	"	"	CH ₂ CO ₂ H
30	237	"	"	"	CH ₂ SCH ₃

2360P/0840A

2361P/0840A

-166-

16622IH

	238	"	"	"	CH_2SOCH_3
	239	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
5	240	"	"	"	SO_2CH_3
	241	"	"	"	SOCH_3
10	242	"	"	"	
	243	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
15	244	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
	245	"	"	"	CH_2OCH_3
20	246	"	"	"	
	247	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
25	248	"	"	"	CF_3
	249	"	"	"	
30	250	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$

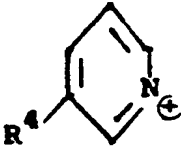
0170073

2360P/0840A

2361P/0840A

-167-

16622IH

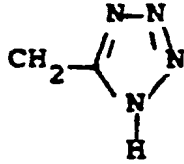
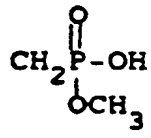
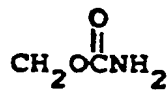
5	251	"		"	CO ₂ H
	252	"		"	CONH ₂
	253	"		"	CN
	254	"		"	OH
	255	"		"	SO ₂ NH ₂
10	256	"	"	"	SO ₃ H
	257	"	"	"	NMe ₂
	258	"	"	"	CONMe ₂
	259	"	"	"	CH ₂ NMe ₂
	260	"	"	"	CH ₂ CN
20	261	"	"	"	CH ₂ CONH ₂
	262	"	"	"	CH ₂ CO ₂ H
	263	"	"	"	CH ₂ SCH ₃
	264	"	"	"	CH ₂ SOCH ₃
		"	"	"	
30		"	"	"	
		"	"	"	
		"	"	"	
		"	"	"	
		"	"	"	

2360P/0840A

2361P/0840A

-168-

16622IH

	265	"	"	"	$\text{CH}_2\text{SO}_2\text{CH}_3$
	266	"	"	"	SO_2CH_3
5	267	"	"	"	SOCH_3
	268	"	"	"	
10					
	269	"	"	"	$\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$
	270	"	"	"	$\text{CH}_2\text{SO}_3\text{H}$
15	271	"	"	"	CH_2OCH_3
	272	"	"	"	
20					
	273	"	"	"	$\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$
	274	"	"	"	CF_3
25					
	275	"	"	"	
	276	"	"	"	$\text{CH}_2\text{SO}_2\text{NH}_2$
30					

0170073

2360P/0840A
2361P/0840A

-169-

16622IH

	277	"	"	"	Br
	278	"	"	"	Cl
5	279	"	"	"	F

10

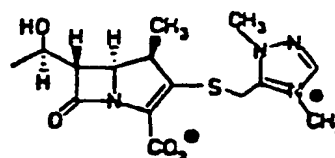
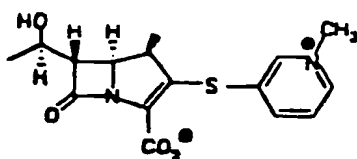
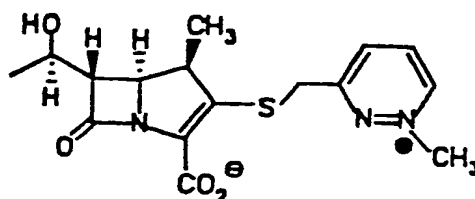
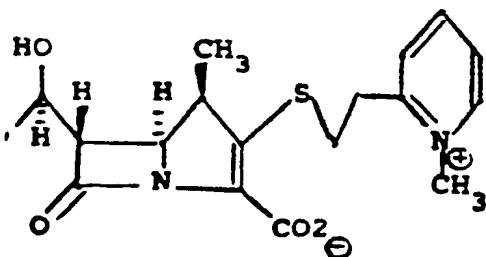
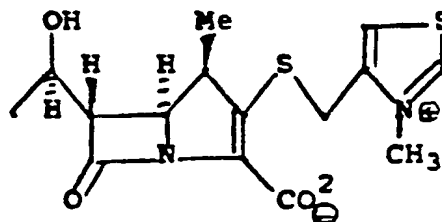
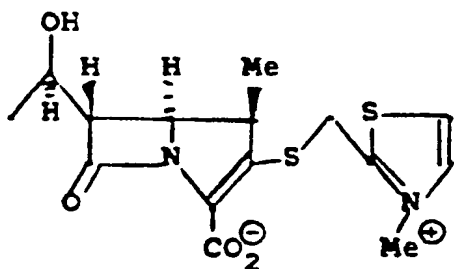
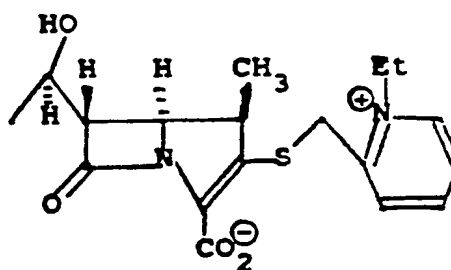
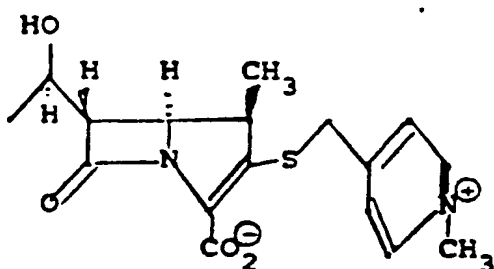
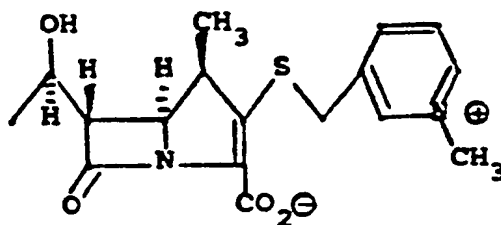
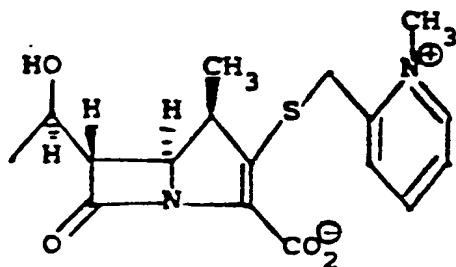
15

20

25

30

8. A compound of Claim 1 wherein the compound is a member selected from the group consisting of:



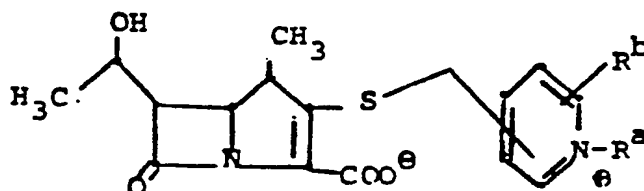
9. The combination of a compound of Claim 1 and a DHP inhibitor.

10. A combination of Claim 10 wherein the DHP inhibitor is 7-(1-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid.

11. A pharmaceutical composition for antibiotic use comprising an antibacterially effective amount of a compound of Claim 1, an inhibitorily effective amount of a DHP inhibitor, and, optionally, a pharmaceutically acceptable carrier.

12. A pharmaceutical composition according to Claim 12 wherein the DHP inhibitor is 7-(1-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid.

13. A compound of Claim 1 of the structure:



wherein

R^a is C₁₋₄ alkyl; or an acidic side-chain of the structure - (CH₂)_n-X-(CH₂)_m-Y-A where:

n = 0-4

m = 0-4

X = CHR³, CH=CH, phenylene (-C₆H₄-), NH, N(C1-C4 alkyl), O, S, S=O, C=O, SO₂, SO₂NH, CO₂, CONH, OCO₂, OC=O, NHC=O;

R³ = H, O(C1-C4 alkyl), NH₂, NH(C1-C4 alkyl), N(C1-C4 alkyl)₂, CN, CONH₂, CON(C1-C4 alkyl)₂, CO₂H, SO₂NH₂, SO₂NH(C1-C4 alkyl);

Y = single bond, NH, N(C1-C4 alkyl), O, S; and

A = an acidic function .

R^b is hydrogen; cyano; or an acidic side-chain
of the structure $-A$ or $-(CH_2)_n-X-(CH_2)_m-Y-A$

where

$n = 0-4$

5 $m = 0-4$

$X = CHR^s, CH=CH, \text{phenylene } (-C_6H_4-), NH, N(C1-C4 \text{ alkyl}), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;$

10 $R^s = H, O(C1-C4 \text{ alkyl}), NH, NH(C1-C4 \text{ alkyl}), N(C1-C4 \text{ alkyl})_2, CN, CONH, CON(C1-C4 \text{ alkyl})_2, CO_2H, SO_2NH_2, SO_2NH(C1-C4 \text{ alkyl});$

$Y = \text{single bond}, NH, N(C1-C4 \text{ alkyl}), O, S; \text{ and}$

$A = \text{an acidic function}.$

15 provided that R^a or R^b must be an acidic side-chain.

14. A compound of Claim 13 wherein the acidic
function $-A$ is a member selected from the group
consisting essentially of carboxy (CO_2H), phosphono [$P=O(OH)_2$],
20 alkylphosphono [$P=O(OH)(O(C1-C4 \text{ alkyl}))$], alkylphosphinyl [$P=O(OH)(C1-C4 \text{ alkyl})$], substituted phosphoramido [$P=O(OH)NH(C1-C4 \text{ alkyl})$] and
 $P=O(OH)NHR^x$], sulfinio (SO_2H), sulfo (SO_3H), 5-tetrazolyl (CN_4H),
arylsulfonamido (SO_2NHR^x) and acylsulfonamides represented by the structures
25 $CONHSO_2(C1-C4 \text{ alkyl}), CONHSO_2N(C1-C4 \text{ alkyl}), SO_2NHCO(C1-C4 \text{ alkyl})$ and
 SO_2NHCOR^x wherein $R^x = \text{aryl or heteroaryl}.$

15. A pharmaceutical composition for antibiotic
use comprising an antibacterially effective amount of
30 a compound of Claim 14, an inhibitorily effective amount
of a DHP inhibitor, and, optionally, a pharmaceutical
carrier.



European Patent
Office

EUROPEAN SEARCH REPORT

0170073

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 85108132.3
Category	Citation of document with indication where appropriate of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	DE - A1 - 3 334 937 (BRISTOL-MYERS CO.) * Claims 1,146,159-163,167 *	1-8,13,14	C 07 D 487/04 A 61 K 31/40 C 07 D 519/00
Y	* Claim 167 *	9-12,15	
	--		
D,Y	EP - A1 - 0 007 614 (MERCK & CO. INC.) * Claims 1,7; page 17, lines 5, 6 *	9-12,15	
	--		
D,Y	EP - A1 - 0 072 014 (MERCK & CO. INC.) * Claims 1,7,14 *	9-12,15	
	--		
A	EP - A1 - 0 021 082 (MERCK & CO. INC.) * Claims 1,3,5 *	1-8,11,13-15	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 D 487/00 A 61 K 31/00 C 07 D 519/00

The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 25-09-1985	Examiner PETROUSEK
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO Form 1503 (03/82)